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(71) Applicant *(for all designated States except US)*: **NEUROSEARCH A/S** [DK/DK]; 93 Pederstrupvej, DK-2750 Ballerup (DK).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **DAHL, Bjarne, H.** [DK/DK]; Rådyrvænget 46, DK-3450 Allerød (DK). **CHRISTOPHERSEN, Palle** [DK/DK]; Axel Juels Allé 48, DK-2750 Ballerup (DK). **ENGSIG, Michael, Thyrring** [DK/DK]; Stengårds Allé 8, st., 0006, DK-2800 Kongens Lyngby (DK). **KARSDAL, Morten, Asser** [DK/DK]; Drejøgade 39, 4 tv, DK-2100 København Ø (DK). **FOGED, Niels, Tækker** [DK/DK]; Damvadvej 30, DK-3670 Veksø (DK). **JENSEN, Flemming, Reissig** [DK/DK]; Gustav Adolfs Gade 14, 4., DK-2100 København Ø (DK).

(74) Common Representative: **NEUROSEARCH A/S**; Patent Department, 93 Pederstrupvej, DK-2750 Ballerup (DK).

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(54) Title: DIARYLUREA DERIVATIVES AND THEIR USE AS CHLORIDE CHANNEL BLOCKERS

(57) Abstract: The present invention relates to novel diarylurea derivatives useful as chloride channel blockers. In other aspects the invention relates to the use of these compounds in a method for therapy, such as for the treatment of bone metabolic diseases, diseases responsive to modulation of the mast cell or basophil activity, diseases responsive to inhibition of angiogenesis, or sickle cell anaemia, and to pharmaceutical compositions comprising the compounds of the invention.

DIARYLUREA DERIVATIVES AND THEIR USE AS CHLORIDE CHANNEL BLOCKERS

TECHNICAL FIELD

The present invention relates to novel diarylurea derivatives useful as chloride channel blockers.

In other aspects the invention relates to the use of these compounds in a method for therapy, such as for the treatment of bone metabolic diseases, diseases responsive to modulation of the mast cell or basophil activity, diseases responsive to inhibition of angiogenesis, or sickle cell anaemia, and to pharmaceutical compositions comprising the compounds of the invention.

BACKGROUND ART

Chloride channels serve a wide variety of specific cellular functions and contribute to the normal function of i.a. skeletal and smooth muscle cells. Chloride channels are probably found in every cell, from bacteria to mammals. Their physiological tasks range from cell volume regulation to stabilization of the membrane potential, transepithelial or transcellular transport and acidification of intracellular organelles.

WO 97/45400, WO 98/47879, WO 00/20378 and WO 00/24707 (all NeuroSearch A/S) describe compounds, such as substituted phenyl derivatives, active as chloride channel blockers.

However, there is a strong interest in the provision of more effective and selective compounds with fewer side effects for the treatment of patients with an osteoclast related bone disease, such as osteoporosis.

Also, there is a strong interest in the provision of more effective and selective compounds with fewer side effects for the treatment of patients with diseases responsive to modulation of the mast cell or basophil activity, diseases responsive to inhibition of angiogenesis, or sickle cell anaemia.

SUMMARY OF THE INVENTION

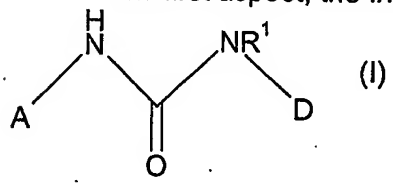
It is an object of the invention to provide novel compounds which act as chloride channel blockers.

A further object of the invention is the provision of compounds with a better selectivity. A still further object is the provision of compounds with a better potency.

A further object of the invention is the provision of compounds that act on cell or tissue specific chloride channels, such as such as chloride channels of osteoclasts. A still further object of the invention is the provision of compounds that act on cell or tissue specific chloride channels, such as such as chloride channels of mast cells or basophils. A further object is the provision of compounds that act on specific groups or subtypes of chloride channels.

A still further object is the provision of compound with more optimal pharmacodynamic properties such as kinetic behaviour, bioavailability, solubility and efficacy.

In its first aspect, the invention provides a compound of general formula I,



(I)

or a pharmaceutically acceptable salt thereof, wherein A, R^1, and D are as defined below.

In its second aspect, the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

In a further aspect, the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the blockade of chloride channels.

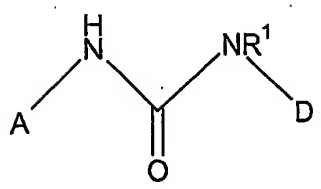
In a still further aspect, the invention relates to a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to blockade of chloride channels, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

Diarylurea derivatives

In its first aspect, the invention provides a compound of general formula I,



(I)

or a pharmaceutically acceptable salt thereof, wherein

A represents a ring system selected from the group consisting of:

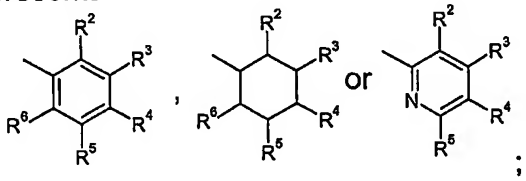
cyclohexanyl, phenyl, pyridyl, thienyl, thiazolyl, naphthyl, indolyl, pyrazolyl and oxo-pyrrolidinyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, nitro, alkyl, alkoxy, and phenyl; and

R^1 represents -H; and

D represents



;

wherein

one of R^2, R^3, and R^4 is selected from the group consisting of:

tetrazolyl, $-COOR^a$, $-B(OH)_2$, $-PO(OR^a)_2$, $-CH_2-PO(OR^a)_2$, and -CONH;

wherein R^a is hydrogen or alkyl:

or R^2 and R^3 or R^3 and R^4 both represent fluoro; and

R^5, R^6 and the remaining one or two of R^2, R^3 and R^4 independently of each other represent:

- hydrogen, halo, trifluoromethyl,
- $-CH=CH-COOR^b$, $-CH_2-CH_2-COOR^b$,
- $-CO-NR^b-CH_2-COOR^c$; $-CO-NR^bR^c$,
- $-CH=CH-CO-NR^bR^c$; $-CH_2-CH_2-CO-NR^bR^c$,
- piperidylcarbonyl,
- $-NH-CO-R^d$ or $-NH-CO-NH-R^d$;

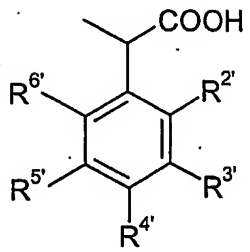
wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halo or trifluoromethyl; or

- phenyl optionally substituted with $-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl;

or R^1 represents -H; and

D represents



wherein $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, $R^{6'}$ independently of each other represent hydrogen, halo, or trifluoromethyl:

or R^1 together with D forms $-CHR^e-CH_2-CHR^f-CH_2-$;

wherein R^e represents -COOH;

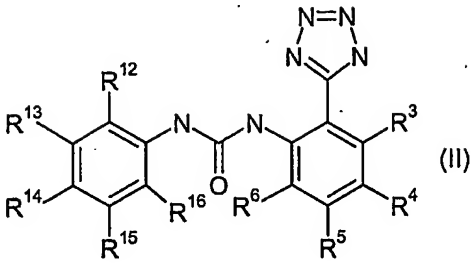
R^f represents hydrogen or hydroxy.

In one embodiment of the compound of general formula I, one of R^2, R^3 and R^4 represents tetrazolyl, such as 1*H*-tetrazol-5-yl. In a special embodiment, R^2 represents tetrazolyl, such as 1*H*-tetrazol-5-yl. In a further special embodiment, R^3 represents tetrazolyl, such as 1*H*-tetrazol-5-yl. In a further special embodiment, R^4 represents tetrazolyl, such as 1*H*-tetrazol-5-yl. In a further embodiment of the compound of general formula I, R^2 represents halo, such as bromo. In a further embodiment of the compound of general formula I, R^2 and R^3 both represent halo, such as bromo.

In a further embodiment of the compound of general formula I, A is selected from the group consisting of: 1*H*-indol-2-yl, cyclohexyl, napthyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, thiophen-2-yl, thiazol-2-yl, thiazol-3-yl, 2*H*-1λ^4-thiazol-2-yl, 3,6-dichloro-pyridin-4-yl, 2,6-dichloro-pyridin-4-yl, 5-chloro-pyridin-2-yl, 2-chloro-pyridin-3-yl, 5-phenyl-2*H*-pyrazol-3-yl, and 5-oxo-1-phenyl-pyrrolidin-3-yl.

In a further embodiment of the compound of general formula I, A is selected from the group consisting of: phenyl, 2-chloro-phenyl, 2-fluoro-phenyl, 2-bromo-phenyl, 2-methoxy-phenyl, 2-trifluoromethyl-phenyl, 2,3-dichloro-phenyl, 2,4,6-trichloro-phenyl, 2,6-dichloro-phenyl, 3-bromo-phenyl, 3-chloro-phenyl, 3-iodo-phenyl, 3-methoxy-phenyl, 3-nitro-phenyl, 3,4-dichloro-phenyl, 3-fluoro-4-chloro-phenyl, 3-nitro-4-chloro-phenyl, 3-trifluoromethyl-4-chloro-phenyl, 3-trifluoromethyl-4-fluoro-phenyl, 3,5-dichloro-phenyl, 3,5-difluoro-phenyl, 3-fluoro-5-trifluoromethyl-phenyl, 3,5-dimethyl-phenyl, 3,5-dimethoxy-phenyl, 3,5-bis-trifluoromethyl-phenyl, 4-chloro-phenyl, 4-methoxy-phenyl, 4-butoxy-phenyl, and 4-phenyl-phenyl.

In a further embodiment of the compound of general formula I, the compound is a compound of general formula (II)



(II)

or a pharmaceutically acceptable salt thereof, wherein

R^3, R^4, R^5 and R^6 independently of each other represent:

- hydrogen, halo, trifluoromethyl,
- $-CH=CH-COOR^b$, $-CH_2-CH_2-COOR^b$,
- $-CO-NR^b-CH_2-COOR^c$; $-CO-NR^bR^c$,
- $-CH=CH-CO-NR^bR^c$; $-CH_2-CH_2-CO-NR^bR^c$,
- piperidylcarbonyl,
- $-NH-CO-R^d$ or $-NH-CO-NH-R^d$;

  wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halo or trifluoromethyl; or
- phenyl optionally substituted with

  $-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl; and

R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} independently of each other represent hydrogen, halo, trifluoromethyl, nitro, alkyl, or alkoxy.

In one embodiment of the compound of general formula II, R^{12} represents hydrogen. In a further embodiment, R^{12} represents halo, such as chloro, fluoro, or bromo. In a further embodiment, R^{12} represents alkoxy, such as methoxy. In a further embodiment, R^{12} represents trifluoromethyl.

In a further embodiment of the compound of general formula II, R^{13} represents halo, such as chloro, fluoro, bromo or iodo. In a further embodiment, R^{13} represents trifluoromethyl. In a further embodiment, R^{13} represents alkoxy, such as methoxy. In a further embodiment, R^{13} represents nitro. In a further embodiment, R^{13} represents alkyl, such as methyl. In a further embodiment, R^{13} represents hydrogen.

In a further embodiment of the compound of general formula II, R^{14} represents halo, such as chloro. In a further embodiment, R^{14} represents hydrogen. In a further embodiment, R^{14} represents alkoxy, such as methoxy or butoxy. In a further embodiment, R^{14} represents phenyl.

In a further embodiment of the compound of general formula II, R^{15} represents halo, such as fluoro or chloro. In a further embodiment, R^{15} represents trifluoromethyl. In a further embodiment, R^{15} represents hydrogen. In a further embodiment, R^{15} represents trifluoromethyl.

In a further embodiment of the compound of general formula II, R^{16} represents hydrogen. In a further embodiment of the compound of general formula II, R^{16} represents halo, such as chloro.

In a further embodiment of the compound of general formula II, R^{12}, R^{14} and R^{16} each represents hydrogen. In a further embodiment of the compound of general formula II, R^{12}, R^{15} and R^{16} each represents hydrogen.

In a further embodiment of the compound of general formula II, R^5 represents halo, such as chloro, and R^2, R^3, R^4 and R^6 each represent hydrogen.

In a still further embodiment of the compound of general formula II, R^4 and R^6 each represent halo, such as bromo or chloro, and R^2, R^3, and R^5 each represent hydrogen. In a special embodiment R^4 and R^6 each represent bromo. In a further special embodiment R^4 and R^6 each represent chloro.

In a still further embodiment of the compound of general formula II, R^4 and R^6 each represent halo, such as bromo or chloro; R^2, R^3, and R^5 each represent hydrogen; two or three of R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} independently of each other represent halo, such as chloro or fluoro; and the remaining three or two of R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} represent hydrogen. In a special embodiment, R^{12} and R^{16} independently represent chloro or fluoro; and R^{13}, R^{14} and R^{15} represent hydrogen. In a further special embodiment, R^{13} and R^{15} independently represent chloro or fluoro; and R^{12}, R^{14} and R^{16} represent hydrogen. In a still further special embodiment, R^{13} and R^{14} independently represent chloro or fluoro; and R^{12}, R^{12} and R^{15} represent hydrogen. In a further special embodiment, R^{12}, R^{14} and R^{16} independently represent chloro or fluoro; and R^{13} and R^{15} represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents $-CO-NR^bR^c$, such as $-CO-NHCH_3$, $-CO-N(CH_3)_2$ or $-CO-N(CH_2CH_3)_2$, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents $-CO-NR^b-CH_2-COOR^c$, such as $-CO-NH-CH_2-COOH$, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents $-CH=CH-COOR^b$, such as $-CH=CH-COOH$, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents $-CH_2-CH_2-COOR^b$, such as $-CH_2-CH_2-COOH$, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents $-CH_2-CH_2-CO-NR^bR^c$, such as $-CH_2-CH_2-CO-NHCH_3$, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents -CH=CH-CO-NR^bR^c, such as -CH=CH-CO-$N(CH_3)_2$ or -CH=CH-CO-$NHCH_3$, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents piperidylcarbonyl, such as 1-piperidylcarbonyl, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula II, R^4 represents phenyl substituted with -SO_2-NR^bR^c, such as -$SO_2N(CH_3)_2$, and R^2, R^3, R^5 and R^6 each represent hydrogen. In a special embodiment, R^4 represents 4-(*N,N*-dimethyl-sulfamoyl)-phenyl.

In a still further embodiment of the compound of general formula II, R^4 represents phenyl substituted with -CO-NR^bR^c, such as -CO-$N(CH_3)_2$, -CO-$NHCH_3$ or -CO-NH_2, and R^2, R^3, R^5 and R^6 each represent hydrogen. In a special embodiment, R^4 represents 4-(*N,N*-dimethyl-carbamoyl)-phenyl, 4-(*N*-methyl-carbamoyl)-phenyl or 4-carbamoyl-phenyl.

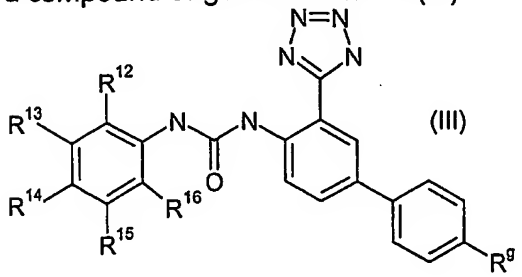
In a still further embodiment of the compound of general formula II, R^4 represents phenyl substituted with -CO-NR^b-CH_2-$COOR^c$, such as -CO-NH-CH_2-COOH or -CO-$N(CH_3)$-CH_2-COOH, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a still further embodiment of the compound of general formula II, R^4 represents phenyl substituted with piperidylcarbonyl, such as 1-piperidylcarbonyl, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a still further embodiment of the compound of general formula II, R^4 represents -NH-CO-R^d, such as -NH-CO-phenyl, and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a still further embodiment of the compound of general formula II, R^4 represents -NH-CO-NH-R^d; such as -NH-CO-NH-(3,5-bis-trifluoromethylphenyl), and R^2, R^3, R^5 and R^6 each represent hydrogen.

In a further embodiment of the compound of general formula I, the compound is a compound of general formula (III)



or a pharmaceutically acceptable salt thereof, wherein
R^g represents -CO-NR^bR^c, -CO-NR^b-CH_2-$COOR^c$, or piperidylcarbonyl;
wherein R^b and R^c independently are hydrogen or alkyl;
two of R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} independently of each other represent

halo, trifluoromethyl, nitro, alkyl, or alkoxy;
and the remaining three of R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} represent hydrogen.

In one embodiment of the compound of general formula III, R^{13} and R^{15} represent trifluoromethyl and R^{12}, R^{14} and R^{16} each represents hydrogen.

In a second embodiment of the compound of general formula III, R^{13} and R^{15} represent halo, such as chloro or fluoro, and R^{12}, R^{14} and R^{16} each represents hydrogen.

In a further embodiment of the compound of general formula III, R^{13} and R^{14} represent halo, such as chloro, or trifluoromethyl, and R^{12}, R^{15} and R^{16} each represents hydrogen. In a special embodiment, R^{13} represents trifluoromethyl and R^{14} represents chloro. In a further special embodiment, R^{13} represents chloro and R^{14} represents trifluoromethyl.

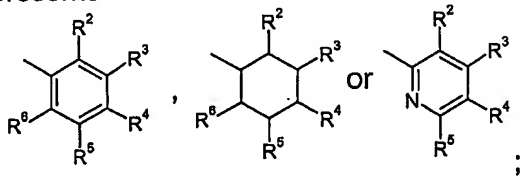
In a further embodiment of the compound of general formula III, R^g represents $-CO-NR^bR^c$, such as $-CO-NH_2$ or $-CO-N(CH_3)_2$.

In a further embodiment of the compound of general formula III, R^g represents $-CO-NR^b-CH_2-COOR^c$, such as $-CO-NH_2-CH_2-COOH$ or $-CO-NHCH_3-CH_2-COOH$.

In a further embodiment of the compound of general formula III, R^g represents piperidylcarbonyl, such as 1-piperidylcarbonyl.

In a still further embodiment of the compound of general formula III, R^g represents $-CO-NR^bR^c$, such as $-CO-N(CH_3)_2$; R^{13} and R^{15} represent halo, such as chloro or fluoro; and R^{12}, R^{14} and R^{16} each represents hydrogen.

In a further embodiment of the compound of general formula I,
A represents a ring system selected from the group consisting of:
cyclohexanyl, phenyl, pyridyl, thienyl, thiazolyl, and pyrazolyl;
which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:
halo, trifluoromethyl, nitro, alkyl, alkoxy, and phenyl; and
R^1 represents -H; and
D represents



;

wherein
R^2 represents $-COOR^a$;
wherein R^a is hydrogen or alkyl;
R^3, R^4, R^5, and R^6 independently of each other represent:

- hydrogen, halo, trifluoromethyl,
- $-NH-CO-R^d$ or $-NH-CO-NH-R^d$;
  wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halo or trifluoromethyl; or
- phenyl optionally substituted with
  $-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl.

In one embodiment of D, R^5 represents halo, such as chloro, bromo or iodo, and R^3, R^4, and R^6 each represent hydrogen.

In a second embodiment of D, R^4 represents halo, such as bromo or chloro, and R^3, R^5, and R^6 each represent hydrogen.

In a further embodiment of D, R^3, R^4, R^5, and R^6 each represent hydrogen.

In a further embodiment of D, R^4 and R^6 represent halo, such as bromo or chloro, and R^3 and R^5 represent hydrogen.

In a further embodiment of D, R^2 represents -COOH or $-COOCH_3$.

In a further embodiment of D, R^4 represents phenyl, and R^3, R^5, and R^6 each represent hydrogen.

In a further embodiment of D, R^5 represents phenyl, and R^3, R^4, and R^6 each represent hydrogen.

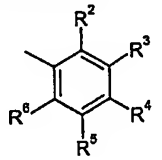
In a further embodiment of D, R^2 represents -COOH; R^4 and R^6 represent halo, such as bromo or chloro, and R^3 and R^5 represent hydrogen.

In a special embodiment, D represents 2-carboxyphenyl, 2-carboxy-4-bromophenyl, 2-carboxy-4-chlorophenyl, 2-carboxy-4-phenylphenyl, 2-carboxy-4,6-dichlorophenyl, 2-carboxy-5-chlorophenyl, 2-carboxy-5-iodophenyl, 2-carboxy-5-phenylphenyl, 2-carboxycyclohexyl, 3-carboxypyridin-2-yl, 3-carboxy-5-bromopyridin-2-yl, 2-methoxycarbonyl-5-chlorophenyl, or 2-methoxycarbonyl-4-bromorophenyl.

In a special embodiment of the compound of general formula I,

A represents a phenyl optionally substituted with one or more substituents independently selected from the group consisting of halo and trifluoromethyl; and

D represents



;

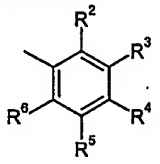
wherein R^2 represents -COOH; R^4 and R^6 represent halo, such as bromo or chloro, and R^3 and R^5 represent hydrogen.

In a further embodiment of the compound of general formula I,

A represents a phenyl optionally substituted with one or more substituents independently selected from the group consisting of

halo and trifluoromethyl; and

D represents



;

wherein

R^3 represents -$COOR^a$;

wherein R^a is hydrogen or alkyl;

R^2, R^4, R^5, and R^6 independently of each other represent

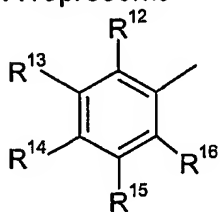
- hydrogen, halo, or trifluoromethyl; or
- -NH-CO-NH-R^d;

  wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halo or trifluoromethyl.

In a special embodiment, D represents 2,5-chloro-3-carboxyphenyl, 3-carboxy-5-trifluoromethylphenyl, 3-carboxy-5-(3-bromo-phenylureido)-phenyl, or 3-carboxy-5-(3,5-dichloro-phenylureido)-phenyl.

In a further embodiment of the compound of general formula I,

A represents



wherein R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} independently of each other represent:

halo, trifluoromethyl, nitro, alkyl, alkoxy, or phenyl.

In a special embodiment R^{13} and R^{15} represent trifluoromethyl and R^{12}, R^{14}, and R^{16} each represent hydrogen.

In a further embodiment of the compound of general formula I,

A represents a ring system selected from the group consisting of:

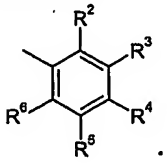
cyclohexanyl, phenyl, and pyridyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, nitro, alkyl, and alkoxy; and

R^1 represents -H; and

D represents



;

wherein

R^2 represents $-B(OH)_2$, $-PO(OR^a)_2$, $-CH_2-PO(OR^a)_2$, or -CONH;

wherein R^a is hydrogen or alkyl (hydrogen, methyl, ethyl);

R^2, R^3, R^4, R^5, and R^6 independently of each other represent:

hydrogen, halo, trifluoromethyl, or phenyl.

In one embodiment of D, R^2 represents $-B(OH)_2$. In a second embodiment I D, R^2 represents $-PO(OR^a)_2$. In a further embodiment of D, R^2 represents $-CH_2-PO(OR^a)_2$. In a further embodiment of D, R^2 represents -CONH.

In a further embodiment of D, R^3, R^4, R^5, and R^6 each represent hydrogen.

In a special embodiment, D represents 2-dihydroborylphenyl, 2-phosphonophenyl, 2-phosphonomethylphenyl, 2-phosphono-4-bromophenyl, 2-phosphonomethyl-4-bromophenyl, 2-phosphonomethyl-4-chlorophenyl, 2-diethylphosphonophenyl, 2-dimethylphosphonomethylphenyl, 2-dimethylphosphonomethyl-4-chlorophenyl, or 2-diethylphosphono-4-bromophenyl.

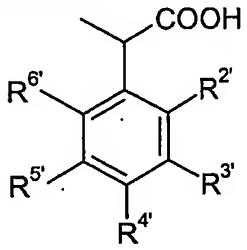
In a further embodiment of the compound of general formula I,

A represents phenyl optionally substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, nitro, alkyl, and alkoxy;

R^1 represents -H; and

D represents



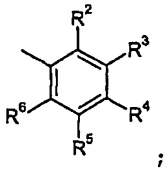
wherein $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, $R^{6'}$ independently of each other represent hydrogen, halo, or trifluoromethyl.

In a special embodiment, D represents α-carboxy-4-fluorobenzyl or α-carboxy-4-trifluoromethylbenzyl.

In a further embodiment of the compound of general formula I,
A represents a ring system selected from the group consisting of:
cyclohexanyl, phenyl, and pyridyl;
which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:
halo, trifluoromethyl, nitro, alkyl, and alkoxy; and
R^1 together with D forms $-CHR^e-CH_2-CHR^f-CH_2-$;
wherein R^e represents -COOH;
R^f represents hydrogen or hydroxy.

In one embodiment, R^f represents hydrogen. In a second embodiment, R^f represents hydroxy.

In a further embodiment of the compound of general formula I,
A represents a ring system selected from the group consisting of:
cyclohexanyl, phenyl, and pyridyl;
which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:
halo, trifluoromethyl, nitro, alkyl, and alkoxy;
R^1 represents -H; and
D represents



;

wherein
R^2 and R^3 or R^3 and R^4 both represent fluoro; and
R^5, R^6 and the remaining one or two of R^2, R^3 and R^4 independently of each other represent hydrogen, halo, or trifluoromethyl.

In one embodiment of D, R^2 and R^3 both represent fluoro.

In a second embodiment, R^4, R^5 and R^6 each represent hydrogen.

In a further embodiment, R^4 represents trifluoromethyl and R^5 and R^6 represent hydrogen.

In a special embodiment, D represents 2,3-difluorophenyl or 2,3-difluoro-4-trifluoromethylphenyl.

In a still further embodiment of the compound of general formula I,
A represents a ring system selected from the group consisting of:

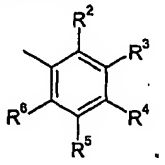
cyclohexanyl, pyridyl, and naphthyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, nitro, alkyl, and alkoxy;

R^1 represents -H; and

D represents



;

wherein

R^2 represents tetrazolyl;

R^3, R^4, R^5, and R^6 independently of each other represent:

- hydrogen, halo, trifluoromethyl; or
- phenyl substituted with
  $-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl, such as methyl.

In a special embodiment, A is selected from cyclohexanyl, 2,6-dichloro-pyridin-4-yl, pyridin-3-yl and 3-naphthalen-1-yl; and D is selected from 3-chloro-6-(1*H*-tetrazol-5-yl)phenyl, 4-bromo-2-1*H*-tetrazol-5-yl)phenyl, and 4'-(*N*,*N*-dimethyl-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl.

In a special embodiment the compound of the invention is

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[2-bromo-4-(1*H*-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[2,6-dibromo-3-(1*H*-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[2-bromo-5-(1*H*-tetrazol-5-yl)-phenyl] urea;

5-Chloro-2-[3-(1*H*-indol-2-yl)-ureido]-benzoic acid;

5-Bromo-2-[3-(1*H*-indol-2-yl)-ureido]-benzoic acid;

N-(3-Fluoro-5-trifluoromethyl-phenyl)-*N'*-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea;

N-(3,5-Difluoro-phenyl)-*N'*-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;

N-(3-Bromo-phenyl)-*N'*-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Dichloro-phenyl)-*N'*-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;

N-(3-Chloro-phenyl)-*N*´-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N*´-[2,4-dibromo-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,4-Dichloro-phenyl)-*N*´-[2,4-dibromo-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3-Methoxy-phenyl)-*N*´-[4´-(*N*´´,*N*´´-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2-Methoxy-phenyl)-*N*´-[4´-(*N*´´,*N*´´-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Methoxy-phenyl)-*N*´-[4´-(*N*´´,*N*´´-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2-Trifluoromethyl-phenyl)-*N*´-[4´-(*N*´´,*N*´´-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-[4´-(*N*´´,*N*´´-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[2,4-dibromo-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-*N*´-[4´-(piperidine-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl)-*N*´-[2,4-dichloro-5-(1*H*-tetrazol-5yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[4-(*N*´´-methyl-carboxamide)- 2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4-(*N*´´-methyl-carboxamide)- 2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-[4-(carbonyl-amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-[4-(acrylic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[4-(acrylic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[4-(acrylic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4-(acrylic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-*N*´-[4-(acrylic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoro-phenyl)-*N*´-[4-(propionic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[4-(propionic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[4-(propionic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4-(propionic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-*N*´-[4-(propionic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[4-(*N*´´-malonamic acid)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[4-(*N*-malonamic acid)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4-(*N*´´-malonamic acid)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-*N*´-[4-(*N*´´-malonamic acid)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-{4-[(*N*´´,*N*´´-dimethyl)-acrylamide]-2-(1*H*-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Difluoro-phenyl)-*N*´-{4-[(*N*´´,*N*´´-dimethyl)-acrylamide]-2-(1*H*-tetrazol-5-yl)-phenyl} urea;
N-(2-Chloro-phenyl)-*N*´-{4-[(*N*´´,*N*´´-dimethyl)-acrylamide]-2-(1*H*-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Dichloro-phenyl)-*N*´-{4-[(*N*´´-methyl)-acrylamide]-2-(1*H*-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Difluoro-phenyl)-*N*´-{4-[(*N*´´-methyl)-acrylamide]-2-(1*H*-tetrazol-5-yl)-phenyl} urea;
N-(2-Chloro-phenyl)-*N*´-[4-(piperidine-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[4-(*N*´´,*N*´´-diethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[4-(*N*´´,*N*´´-diethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4-(*N*´´,*N*´´-diethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-*N*´-[4-(*N*´´,*N*´´-diethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-[4-(piperidine-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-dichloro-phenyl)-*N*´-[4-(piperidine-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[4-(piperidine-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4-(piperidine-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[4´-(carbonyl-(*N*´´-methyl)amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;

N-(3,5-Dichloro-phenyl)-*N*´-[4-(*N*´´,*N*´´-dimethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4-(*N*´´,*N*´´-dimethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl)-*N*´-[4-(*N*´´,*N*´´-diethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-*N*´-[4´-(carbonyl-amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-[4-(*N*´´-methyl-propylamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[4-(*N*´´-methyl-propyamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluromethyl-phenyl)-*N*´-[4-(*N*´´-methyl-propylamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4-(*N*´´-methyl-propylamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-chloro-phenyl)-*N*´-[4-(*N*´´-methyl-propylamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2,6-Dichloro-phenyl)-*N*´-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2,4,6-trichloro-phenyl)-*N*´-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[4-benzamide-2-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4-benzamide-2-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[4-benzamide-2-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)- *N*´-[4-benzamide-2-(1*H*-tetrazol-5-yl)-phenyl) urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)- *N*´-[4-(*N*´´,*N*´´-dimethyl acryl-amide)-2-(1-*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-dichloro-phenyl)-*N*´-[4-(*N*´´,*N*´´-dimethyl acryl-amide)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-(3-Chloro-4-fluoro-phenyl)-*N*´-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4´-sulfonic acid-dimethylamide] urea;
N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N*´-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4´-sulfonic acid-dimethylamide] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4´-carboxylic acid dimethylamide] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4´-carboxylic acid dimethylamide] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-[4´-(piperidine-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;

N-(3,5-Dichloro-phenyl)-*N*´-[4´-(piperidine-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[4´-(piperidine-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4´-(piperidine-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-[4´-carboxamide-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[4´-carboxamide-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[4´-carboxamide-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4´-carboxamide-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[4´-(carbonyl-amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4´-(carbonyl-amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-{4´-[carbonyl-(*N*´´-methyl)-amino-acetic acid]-2-(1*H*-tetrazol-5-yl)-4-biphenyl} urea;
N-(3,5-Dichloro-phenyl)-*N*´-{4´-[carbonyl-(*N*´´-methyl)-amino-acetic acid]-2-(1*H*-tetrazol-5-yl)-4-biphenyl} urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-{4´-[carbonyl-(*N*´´-methyl)-amino-acetic acid]-2-(1*H*-tetrazol-5-yl)-4-biphenyl} urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4´-(carbonyl-amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[4´-(*N*´´-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-[4´-(*N*´´-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
4-Chloro-2-(3-cyclohexyl-ureido)-benzoic acid;
5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid;
2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid;
5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3-bromo-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid;
N-(3,5-Bis-trifluormethyl-phenyl)-*N*´-(phenyl-2-boronic acid) urea;
N-(4-Chloro-3-fluoro-phenyl)-*N*´-(phenyl-2-boronic acid) urea;
N-(3,5-Dichloro-phenyl)-*N*´-(phenyl-2-boronic acid) urea;
N-Cyclohexyl-*N*´-(phenyl-2-boronic acid) urea;

5-Chloro-2-[3-(pyridin-3-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(pyridin-3-yl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3-chloro-4-fluoro-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(4-fluoro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3-fluoro-5-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
2-[3-(Thiophen-2-yl)-ureido]-benzoic acid;
2-[3-(Pyridin-4-yl)-ureido]-benzoic acid;
4-Chloro-2-[3-(pyridin-4-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(pyridin-4-yl)-ureido]-benzoic acid;
2-[3-(Pyridin-3-yl)-ureido]-nicotinic acid;
2-[(3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[(3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(3,5-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-(3-Cyclohexyl-ureido)-cyclohexanecarboxylic acid;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexane carboxylic acid;
4-Chloro-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3-chloro-phenyl)-ureido]-benzoic acid;
2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
5-Bromo-2-(3-cyclohexyl-ureido)-benzoic acid;
2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(2,6-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexanecarboxylic acid;
4-Chloro-2-[3-(thiazol-2-yl)-ureido]-benzoic acid methyl ester;
5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid methyl ester;
4-Chloro-2-[3-(5-chloro-pyridin-2-yl)-ureido]benzoic acid;
5-Bromo-2-(3-thiazol-2-yl-ureido)-benzoic acid methyl ester;
2-[3-(5-Bromo-pyridin-3-yl)-ureido]-4-chloro-benzoic acid;
5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid;
3-Bromo-2-[3-(2*H*-1λ^4-thiazol-2-yl)-ureido]-benzoic acid;
3-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
4-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Difluoro-phenyl)-ureido]-biphenyl-3-carboxylic acid;

4-[3-(2-Chloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-Chloro-2-[3-(5-phenyl-2*H*-pyrazol-3-yl)-ureido]-benzoic acid;
2-[3-(2-chloro-pyridin-3-yl)-ureido]-nicotinic acid;
4-Chloro-2-[3-(2-chloro-pyridin-3-yl)-ureido]-benzoic acid;
2-[3-(4-Chloro-phenyl)-ureido]-5-iodo-benzoic acid;
5-Chloro-2-[3-(5-oxo-1-phenyl-pyrrolidin-3-yl)-ureido]-benzoic acid;
5-Bromo-2-(3-phenyl-ureido)-benzoic acid;
5-Bromo-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2-bromo-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(4-chloro-3-nitro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(4-butoxide-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid;
2-[3-(4-Biphenyl)-ureido]-5-bromo-benzoic acid;
5-Chloro-2-[3-(3-iodo-phenyl)-ureido]- -benzoic acid;
5-Chloro-2-(3-phenyl-ureido)-benzoic acid;
5-Chloro-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
5-Chloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3,4-dichloro-phenyl)-ureido]-benzoic acid;
2-[3-(4-Butoxy-phenyl)-ureido]-5-chloro- benzoic acid;
5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-nicotinic acid;
3,5-Bis-[3-(3,5-difluro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-nicotinic acid;
5-Bromo-2-[3-(2,4,6-trichloro-phenyl)-ureido]-nicotinic acid;
5-Chloro-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid;
2,5-Dichloro-3-[3-(3-bromo-phenyl)-ureido]-benzoic acid;
2,5-Dichloro-3-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
3,5-Bis-[3-(3-bromo-phenyl)-ureido]-benzoic acid
3,5-Bis-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
3-[3-(3-Bromo-phenyl)-ureido]-5-trifluoro-benzoic acid;
3-[3-(3,5-Dichloro-phenyl)-ureido]-5-trifluoro-benzoic acid;

3,5-Bis-[3-(3,5-bis-trifluoromethylphenyl)-ureido]- benzoic acid;
2-[3-(Pyridin-3-yl)-ureido]-phenyl-boronic acid;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl-boronic acid;
2-[3-(3-Bromo-phenyl)-ureido]-phenyl]-dihydroxy-borane;
{2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
{2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid
{2-[3-(3-chloro-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester;
{2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid;
{2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid;
{2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(3,5 bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid;
2-{[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
2-{[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid;
2-{[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
2-{[3-(3,5-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
2-[(3-Phenyl-ureido)-benzyl]-phosphonic acid dimethyl ester;
2-[(3-Phenyl-ureido)-benzyl]-phosphonic acid;
2-[3-(4-Chloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
2-[3-(4-Chloro-phenyl)-ureido]-benzyl}-phosphonic acid;
2-{[3-(3,4-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
2-{[3-(3,4-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;

{5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid;
{5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
[5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid dimethyl ester;
[5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(4-chloro-phenyl)-ureido]-benzyl}-phosphonic acid;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
{2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid diethyl ester;
{2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester;
{2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid;
3-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
3-[3-(2,3-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
3-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
{2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid;
[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(5-trifluoromethyl-phenyl)-acetic acid;
[3-(4-Chloro-3-fluoro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
[3-(3,5-Dichloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
[3-(3-Chloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-pyrroline-2-carboxylic acid;
1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrroline-2-carboxylic acid;
1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(3-Chloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(3-Bromo-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(3,5-Dichloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(Cyclohexyl-carbamoyl)-pyrrolidine-2-carboxylic acid;
1-(2,6-Dichloro-pyridin-4-ylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
1-(3-Chloro-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
1-(3-Bromo-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
1-(Pyridin-3-ylcarbamoyl)-pyrrolidine-2-carboxylic acid;
N-Cyclohexyl-*N'*-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
N-Cyclohexyl-*N'*-(2,3-difluoro-phenyl) urea;
N-(2,3-Difluoro-4-trifluoromethyl-phenyl)-*N'*-(pyridin-3-yl) urea;
N-(Pyridin-3-yl)-*N'*-(2,3-difluoro-phenyl) urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
N-(2,6-Dichloro-pyridin-4-yl)-*N'*-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
N-(2,3-Difluoro-4-trifluoromehyl-phenyl)-*N'*-(pyridin-4-yl) urea;
N-(2,3-Difluoro-phenyl)-*N'*-(pyridin-4-yl) urea;
N-(Cyclohexyl)-*N'*-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2,6-Dichlooro-pyridin-4-yl)-*N'*-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-Cyclohexyl-*N'*-[4'-(*N''*,*N''*-dimethyl-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2,6-Dichloro-pyridin-4-yl)-*N'*-[4'-(*N''*,*N''*-dimethyl-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-Cyclohexyl-*N'*-[4-bromo-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2,6-Dichloro-pyridin-4-yl)-*N'*-[4-bromo-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-[5-Chloro-2-(1*H*-tetrazol-5-yl)-phenyl]-*N'*-(pyridin-3-yl) urea;
N-[4-Bromo-2-(1*H*-tetrazol-5-yl)-phenyl]-*N'*-(pyridin-3-yl) urea;
N-(Naphthalen-1-yl)-*N'*-[4'-(*N''*,*N''*-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-[2,4-Dibromo-6-(1*H*-tetrazol-5-yl)-phenyl]-*N'*-(2,6-dichloro-pyridin-4-yl) urea;
or a pharmaceutically acceptable salt thereof.

Any combination of two or more of the embodiments described herein is considered within the scope of the present invention.

Definition of Substituents

In the context of this invention halo represents fluoro, chloro, bromo or iodo.

Alkyl means a straight chain or branched chain of one to six carbon atoms, including but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and hexyl; methyl, ethyl, propyl and isopropyl are preferred groups.

Alkoxy is O-alkyl, wherein alkyl is as defined above.

Amino is NH_2 or NH-alkyl or N-$(alkyl)_2$, wherein alkyl is as defined above.

Steric Isomers

The chemical compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms. The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present

invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzensulphonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the

toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

Examples of pharmaceutically acceptable cationic salts of a chemical compound of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the zinc, the aluminium, the lithium, the choline, the lysine, and the ammonium salt, and the like, of a chemical compound of the invention containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art.

In the context of this invention the "onium salts" of N-containing compounds are also contemplated as pharmaceutically acceptable salts (aza-onium salts). Preferred aza-onium salts include the alkyl-onium salts, in particular the methyl- and the ethyl-onium salts; the cycloalkyl-onium salts, in particular the cyclopropyl-onium salts; and the cycloalkylalkyl-onium salts, in particular the cyclopropyl-methyl-onium salts.

Methods of Preparation

The compounds of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of a compound of the invention.

While a compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising a compound of the invention, or a pharmaceutically acceptable salt or

derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof. In a further embodiment, the invention provides pharmaceutical compositions comprising more than one compound/prodrug of the invention, such as two different compounds/prodrugs of the invention.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, pulmonal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

The chemical compound of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The chemical compound of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.

For preparing pharmaceutical compositions from a chemical compound of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending

agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The chemical compound according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations, intended for conversion shortly before use to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. In addition to the active component such preparations may comprise colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the chemical compound of the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Compositions suitable for topical administration in the mouth include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for

example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

A therapeutically effective dose refers to that amount of active ingredient, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED_{50} and LD_{50}, may be determined by standard pharmacological procedures in cell cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by the ratio LD_{50}/ED_{50}. Pharmaceutical compositions exhibiting large therapeutic indexes are preferred.

The dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 μg/kg i.v. and 1 μg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 μg/kg to about 10 mg/kg/day i.v., and from about 1 μg/kg to about 100 mg/kg/day p.o.

Biological Activity

The compounds of the present invention are useful as blockers of chloride channels, such as chloride channels of osteoclasts. In a further embodiment, the compounds of the present invention are useful as blockers of chloride channels of mast cells and basophils. For measuring the activity of the compounds, various in vitro and in vivo methods, such as various osteoclast inhibition assays known in the art can be used.

Methods of Therapy

Compounds that are active as chloride channels blockers are likely to be useful in the treatment of a number of diseases, disorders and conditions, including bone metabolic diseases. Further, compounds that are active as chloride channel blockers are likely to be useful in the treatment of diseases responsive to modulation of the mast cell or basophil activity, diseases responsive to inhibition of angiogenesis, or sickle cell anaemia.

Thus in a further aspect, the compounds of the invention are considered useful for the treatment, prevention or alleviation of a disease, disorder or condition responsive to the blockade of chloride channels.

In a special embodiment, the disease or a disorder or a condition is a bone metabolic disease, such as an osteoclast related bone disease. In a further embodiment, the disease or a disorder or a condition is an osteoclast related bone disease, such as osteoporosis, postmenopausal osteoporosis, secondary osteoporosis, osteolytic breast cancer bone metastasis, osteolytic cancer invation, and Paget's disease of bone.

In a further special embodiment, the disease or a disorder or a condition is responsive to modulation of the mast cell or basophil activity. In a still further embodiment, the disease or a disorder or a condition is responsive to modulation of mast cell or basophil production or secretion of histamine, neutral proteases or tryptases (such as chymotryptases and carboxypeptidases), leukotrienes (such as LTC4, and LTB4), prostaglandins (such as PGD2), TXA2, PAF, or cytokines (such as IL-4 and TNF-α). In a further embodiment, the disorder or disease that is responsive to modulation of the mast cell or basophil activity is a disorder or disease that is responsive to modulation of mast cell or basophil production or secretion of histamine. In a still further embodiment, the disorder or disease that is responsive to modulation of the mast cell or basophil activity is allergic bronchopulmonary aspergillosis (ABPA), allergic rhinitis, allergic skin disease, allergic skin reaction, drug induced allergic skin reaction, anaphylaxis, asthma, atherosclerosis, atopic dermatitis (AD), bronchial asthma, cancer, chronic obstructive pulmonary disease (COPD), Chrohn's disease, contact dermatitis, dilated cardiomyopathy, fatal asthma, graft rejection,

hypersensitivity pneumonitis, ischemic hearth disease, pulmonary fibrosis, rheumatoid arthritis, systemic sclerosis, urticaria, or uveoretinitis. In a special embodiment, the disorder or disease that is responsive to modulation of the mast cell or basophil activity is allergic bronchopulmonary aspergillosis (ABPA), allergic rhinitis, allergic skin disease; allergic skin reaction, drug induced allergic skin reaction, asthma, bronchial asthma, fatal asthma or chronic obstructive pulmonary disease (COPD). In a further special embodiment, the disorder or disease is asthma, bronchial asthma, fatal asthma or chronic obstructive pulmonary disease (COPD). In a further special embodiment, the disorder or disease is COPD. In a still further special embodiment, the disorder or disease is asthma.

In a further special embodiment, the disease or a disorder or a condition is responsive to inhibition of angiogenesis. In a special embodiment, the diseases, disorders or conditions that are responsive to inhibition of angiogenesis are selected from:

- diseases, disorders or conditions that involve the proliferation of tumor cells, such as cancer, prostate cancer, lung cancer, breast cancer, bladder cancer, renal cancer, colon cancer, gastric cancer, pancreatic cancer, ovarian cancer, melanoma, hepatoma, sarcoma and lymphoma;
- ophthalmic angiogenesis related diseases, disorders or conditions, such as exudative macular degeneration, age-related mucular degeneration (AMD), retinopathy, diabetic retinopathy, proliferative diabetic retinopathy, diabetic macular edema (DME), ischemic retinopathy (e.g. retinal vain or artery occlusion), retinopathy of prematurity, neovascular glaucoma, and corneal neovascularization; and
- rheumatoid arthritis, and psoriasis.

In a special embodiment, the disease, disorder or condition to be treated is a preneoplastic disease state. In a further embodiment, the treatment is an anti-metastatic treatment. In a still further embodiment, the disease, disorder or condition to be prevented is metastatic cancer. In a further embodiment, the disease, disorder or condition to be prevented or alleviated is DME.

In the context of this invention, "age-related macular degeneration" (AMD) includes dry AMD (non-exudative AMD) and wet AMD (exudative AMD).

In a still further embodiment, the disease, disorder or condition responsive to the blokade of chloride channels is sickle cell anaemia, brain oedema following ischaemia or tumors, diarrhea, hypertension, diuretic hypertension, glaucoma, or ulcers.

It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject

involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge. When administered in combination with compounds known in the art for treatment of the diseases, the dosis regimen may be reduced.

Use of the compounds of the invention may be combined with the use of one or more additional drugs.

Use of the compounds of the invention may be combined with the use of other bone metabolism controlling compounds for the treatment of bone metabolic disease. Such known bone metabolism controlling compounds include bisphophonates such as etidronate, pamidronate, or clodronate optionally combined with calcium; oestrogen-receptor active compounds such as oestrogen i.e. oestradiol and ethyloestradiol, calcitonin, 1,25-dihydroxyvitamine D and metabolites thereof, fluoride, growth hormone, parathyroid hormone, triiodo-thyrosine, collagen degrading enzymes such as protease inhibitors, or cancer therapeutic agents.

Further, use of the compounds of the invention may be combined with the use of one or more additional drugs useful for the treatment, prevention or alleviation of a disease responsive to inhibition of anglogenesis, such as compounds useful for anti-metastatic treatment. Such additional drugs include cytotoxic compounds, antimitotic compounds, and antimetabolites.

Examples of cytotoxic compounds (including cytotoxic alkylating agents) include carmustine (BCNU), fotemustin, temozolomide (temodal), ifosfamide, and cyclofosfamide.

Examples of antimitotic compounds include paclitaxel (taxol) and docetaxel.

An example of antimetabolites includes methotrexat.

Furthermore, the compounds of the invention may be combined or administered in combination with other treatments or therapies. Examples of other treatments or therapies include radiotherapy and surgery.

The treatment of the diseases and disorder can be in chronical or long term treatment as well as a treatment of sudden crisis in the disease and disorder.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

Example 1

(2-Amino-phenyl)-phosphonic acid diethyl ester

Diethylphosphite (1.5 g, 11 mmol) in liquid ammonia (app. 100 ml) was added potassium tert.-butoxide (1.23 g, 11 mmol), the reaction mixture was stirred for 10 min. before 2-iodoaniline was added. The reaction mixture was irradiated (Hg-lamp) for an

hour. Ammonia was evaporated and ammonium chloride was added with some ammonia, ammonia was evaporated off. The residue was added water and extracted with dichloromethane. The title compound was purified by column chromatography. Yield 1.7 g (yellow oil).

Example 2

(2-Amino-5-bromo-phenyl)-phosphonic acid diethyl ester

(2-Amino-phenyl)-phosphonic acid diethyl ester (0.23g, 1 mmol) in glacial acetic acid (2 ml) under stirring was added bromine (0.16 g, 1 mmol, 1 eq.) in glacial acetic acid (2 ml) over 20 min. After the reaction was completed, the reaction mixture was poured into a saturated aqueous sodium bicarbonate solution. The title compound was extracted with dichloromethane and purified by column chromatography. Yield 0.23 g

Example 3

[(Dimethoxy-phosphoryl)-hydroxy-(2-nitro-phenyl)-methyl]-phosphonic acid dimethyl ester

Trimethyl phosphite (5.7 g, 45.7 mmol) was cooled to –10°C under a argon atmosphere and glacial acetic acid was added (1.44 ml), while keeping the temperature below 0°C, was drop wise added 2-nitrobenzoyl chloride, the reaction mixture was allowed to heat to room temperature and stirred for one hour. At a pressure of 10 mmHg was the reaction mixture heated to 40°C for one hour and cooled to room temperature. Ethyl acetate was added and the solution was washed with 5% sodium bicarbonate (aq.), the organic phase was dried and evaporated, the title compound was purified by column chromatography.

The following compound was made analogously;

[(Dimethoxy-phosphoryl)-hydoxy-(3-chloro-6-nitro-phenyl)-methyl]-phosphonic acid dimethyl ester.

Example 4

5-Amino-furan-2-carboxylic acid

5-Nitro-2-furoic acid methyl ester (14.3 g, 84 mmol) in ethyl acetate (110 ml) was added palladium on charcoal (0.75 g, 5%), the solution was stirred at 40°C under a hydrogen atmosphere for 4 hours, the reaction mixture was filtered through celite, the title compound was isolated by evaporation and used as this in the next reaction.

Example 5

4-Amino-1-hydroxy-cyclohexa-2,4-dienecarboxylic acid methyl ester

5-Amino-furan-2-carboxylic acid (the crude product from example 4) was dissolved in benzene (0.5 L) and added acrylonitrile (200 ml), the reaction mixture was heated at

reflux, stirred for 16 hours and evaporated, the residue was added toluene and evaporated. The title compound was crystallized from ethyl acetate, and used with out further purification in the next reaction.

Example 6

4-Amino-3-cyano-benzoic acid methyl ester

4-Amino-1-hydroxy-cyclohexa-2,4-dienecarboxylic acid methyl ester (the crude product from example 5) was dissolved in toluene (600 ml) and added boron trifluoride diethyl etherate (20 ml of 40% in diethyl ether), the reaction mixture was added tetrahydrofurane (100 ml) and stirred at 85°C for 30 min. The reaction mixture was cooled to room temperature and poured into ice/water, the mixture was neutralized with sodium hydroxide (1 M) and basified with saturated sodium bicarbonate. The layer was separated and the water phase was extracted with dichloro methane. The organic phases was dried and evaporated. The title compound was isolated from the residue by column chromatography. Yield 3.2 g.

Example 7

4-Amino-3-cyano-benzoic acid

4-Amino-3-cyano-benzoic acid methyl ester (3.2 g, 10 mmol) in tetrahydrofurane/ water (110 ml, 1:1) was added lithium hydroxide hydrate (2.3 g, 30 mmol), the reaction mixture was stirred at room temperature for 20 hours and added hydro chloric acid (1 M) to pH = 3. From the mixture was tetrahydrofurane distilled of and the title compound precipitated out of solution.

Example 8

4-Amino-3-cyano-*N*-methyl-benzamide

4-Amino-3-cyano-benzoic acid (0.97 g, 6 mmol), benzotriazol-1-yloxytris-(pyrrolidino)-phosphonium hexafluorophosphate (3.3 g, 6.3 mmol) and diisopropylethylamine (6 ml, 12 mmol) in anhydrous dimethyl formamide (25 ml) was added dimethylamine (6 ml of a 2 M in tetrahydrofurane), the reaction mixture was stirred at room temperature overnight. Some of the dimethyl formamide was evaporated off, the crude product was dissolved in ethyl acetate (25 ml), washed with potassium hydrogen sulphate (twice with 0.5 M (25 ml)), sodium hydroxide (twice with 1 M (25 ml)), water (10 ml) and brine (25 ml). The organic layer was dried and evaporated, the title compound was isolated by column chromatography. Yield 0.39 g.

The following compounds were made analogously:
4-Amino-3-cyano-*N,N*-dimethyl-benzamide;
(4-Amino-3-cyano-benzoylamino)-acetic acid ethyl ester;
2-Amino-5-(piperidine-1-carbonyl)-benzonitrile;

4-Amino-3-cyano-*N,N*-diethyl-benzamide;
[(4-Amino-3-cyano-benzoyl)-methyl-amino]-acetic acid.

Example 9

(2-Amino-benzyl)-phosphonic acid dimethyl ester

[(Dimethoxy-phosphoryl)-hydroxy-(2-nitro-phenyl)-methyl]-phosphonic acid dimethyl ester (4.7 g, 17.7 mmol) in 99% ethyl alcohol (40 ml) was added Tin(II) chloride dihydrate (14.4 g, 64 mmol, 5 eq.), the reaction mixture was heated at 70°C for 20 min. and poured into ice (250 ml), pH was adjusted to 7 with sodium hydroxide (1 M) and ethyl acetate was added, the emulsion was filtered through kieselguhr twice, the organic layer was washed with brine, dried, evaporated and the title compound was isolated as an oil. Yield 2 g.

The following compound was made analogously:
(2-Amino-5-chloro-benzyl)-phosphonic acid dimethyl ester.

Example 10

2-Amino-benzeneboronic acid

2-Nitro-benzeneboronic acid (2.32 g, 14 mmol) in ethyl alcohol (130 ml, 99%) was added palladium on charcoal (0.232 g, 10%), stirred under a hydrogen atmosphere (3 bar) overnight and filtered. The filtrate was evaporated, the title compound was crystallized from methyl alcohol and water. Yield 0.52 g.

Example 11

4-Methyl-phenyl-boronic acid

4-Bromo-toluene (50 g, 0.29 mol) in anhydrous diethyl ether (500 ml) was cooled to -20°C, while keeping the temperature under – 20°C, was butyl lithium (127 ml of an 2.5 M solution in hexane 0.31 mol) added, after 15 min the solution was allowed to heat to 15°C and stirred at that temperature for an hour, then cooled to – 55°C, while keeping the temperature under - 47°C was tributylborate (110 ml, 94 g, 0.41 mol, 1.4 eq.) added, the reaction mixture was allowed to heat to room temperature and stirred overnight. Hydrochloric acid (450 ml of 1 M) was added. The phases were separated, the water phase was extracted with diethyl ether, the organic phases werer combined and extracted with sodium hydroxide (aq.) (300 ml + 2 times with 100ml of 2 M), the water phases were added concentrated hydrochloric acid (app. 100 ml), the title compound precipitated and was isolated by filtration. Yield 32.6 g

Example 12

4-(Dihydroxyboryl) benzoic acid

4-Methyl-phenyl-boronic acid (32.6 g 0.24 mol) was dissolved in water (900 ml) containing sodium hydroxide (19.2 g 0.48 mol, 2 eq.) and added potassium permanganate (79.6 g, 0.5 mol, 2.1 eq.), the reaction mixture was stirred at room temperature for 72 hours and filtered, the precipitate was washed three times with water (50 ml), the filtrate was added concentrated hydrochloric acid (app. 55 ml) and the title compound precipitated. Yield 34.5 g.

Example 13

4-(Dihydroxyboryl)-(*N,N*-dimethylbenzamide)

4-(Dihydroxyboryl) benzoic acid (34.4 g, 0.21 mol) was added to thionyl chloride (300 ml), the reaction mixture was heated at reflux overnight and evaporated to dryness, the residue was added dimethylamine (167 ml of a 40% solution in water), the reaction mixture was heated at reflux for 20 min. and filtered while still hot, the filtrate was cooled to room temperature and added concentrated hydrochloric acid and the title compound precipitated. Yield 25.1 g.

The following compounds were made analogously:
4-(Dihydroxyboryl)-benzamide;
[4-(Dihydroxyboryl)-benzoylamino]-acetic aid;
[4-(Dihydroxyboryl)-benzoyl-(*N*-methyl)-amino]-acetic acid.

Example 14

4′-Amino-3′-cyano-biphenyl-4-carboxylic acid dimethylamide

4-(Dihydroxyboryl)-(*N,N*-dimethylbenzamide) (1.2 g, 6.2 mmol), 2-amino-5-bromobenzonitrile (1.1 g, 5.6 mmol, 0.9 eq), potassium carbonate (2.3g, 16.9 mmol, 3.3 eq.), dimethoxyethylenglycol (20 ml) and water (10 ml) was mixed nitrogen was bobbled through the mixture, bis(triphenylphosphine)palladium (II) chloride (0.05 g) was added, the reaction mixture was heated at reflux for 40 min, cooled to room temperature, added water (50 ml) and extracted with ethyl acetate (50 ml), the organic phase was washed with water (30 ml) dried, evaporated and the title compound was left as an oil. Yield 1.17 g.

Example 15

3-(4-Amino-3-cyano-phenyl)-acrylic acid methyl ester

2-Amino-5-bromo-benzonitrile (0.59 g 3 mmol), methylacrylate (0.52 g, 6 mmol) and tri-o-tolylphosphine (0.49 mg, 0. 16 mmol) in anhydrous *N,N*-dimethyl formamide (5 ml) was added triethylamine (0.44 ml), the mixture was bobbled through with argon and palladium (II) acetate (4.5 mg, 0.02 mmol) and stirred at 120°C for 2.5 hours.

Then the reaction was finished, the reaction mixture was cooled to room temperature and added hydrochloric acid (15 ml of 1 M), the title compound was extracted with diethyl ether (four times with 25 ml), the organic phase was dried and evaporated.

The following compound was made analogously:
3-(Amino-3-cyano-phenyl)-acryl *N,N*-dimethyl amide.

Example 16

3-(4-Amino-3-cyano-phenyl)-propionic acid methyl ester

3-(4-Amino-3-cyano-phenyl)-acrylic acid methyl ester (10 g, 49 mmol) and palladium on charcoal (2 g, 10%) in tetrahydrofurane (200 ml) was stirred vigorously under a hydrogen atmosphere for 20 min., the reaction mixture was filtered though celite and the title compound was isolated by filtration. Yield 10 g

The following compound was made analogously:
3-(4-Amino-3-cyano-phenyl)-propionic acid *N,N*-dimethyl amide.

Example 17

4′-Amino-3′-(1*H*-tetrazol-5-yl)-biphenyl-4-carboxylic acid dimethylamide

4′-Amino-3′-cyano-biphenyl-4-carboxylic acid dimethylamide (1.15 g, 4.3 mmol) in toluene (25 ml) was added sodium azide (0.42 g, 6.5 mmol, 1.5 eq.) and triethylammonium chloride (0.9 g, 6.5 mmol, 1.5 eq.), the reaction mixture was stirred at 60°C for 48 hours. The top phase was decanted from the bottom layer, the residue was added water (25 ml), 96% ethyl alcohol (25 ml) and concentrated hydro chloric acid (app. 1 ml) and the title compound precipitated out. Yield 0.79 g.

The following compounds were made analogously:
4′-Amino-3-(1*H*-tetrazol-5-yl)-biphenyl-4-dimethyl-sulfon-amide;
2-Bromo-4-(1*H*-tetrazol-5-yl)-aniline;
2,6-Dibromo-4-(1*H*-tetrazol-5-yl)-aniline;
2-Bromo-5-(1*H*-tetrazol-5-yl)-aniline;
3-Chloro-6-(1*H*-tetrazol-5-yl)-aniline;
4-Bromo-2-(1*H*-tetrazol-5-yl)-aniline;
2,4-Dibromo-6-(1*H*-tetrazol-5-yl)-aniline;
[4′-Amino-3′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]-carbonyl-piperidin-1-yl;
2,4-Dichloro-6-(tetrazol-5-yl)-aniline;
4-Amino-*N*-methyl-3-(1*H*-tetrazol-5-yl)-benzamide;
[4-Amino-3-(1*H*-tetrazol-5-yl)-benzoylamino]-acetic acid;
3-[4-Amino-3-(1*H*-tetrazol-5-yl)-phenyl]-acrylic acid methyl ester;
3-[4-Amino-3-(1*H*-tetrazol-5-yl)-phenyl]-propionic acid methyl ester;
N-[4-Amino-3-(1*H*-tetrazol-5-yl)-phenyl]-malonamic acid;

3-[4-Amino-3-(1*H*-tetrazol-5-yl)-phenyl]-*N,N*-dimethyl-acrylamide;
3-[4-amino-3-(1*H*-tetrazol-5-yl)-phenyl]-*N*-methyl-acrylamide;
4-Amino-*N,N*-diethyl-3-(1*H*-tetrazol-5-yl)-benzamide;
4-Amino-3-(1*H*-tetrazol-5-yl)-benzoyl-piperidin-1-yl;
4′-Amino-3′-(1*H*-tetrazol-5-yl)-biphenyl-4-carboxylic acid amide;
4-Amino-*N,N*-dimethyl-3-(1*H*-tetrazol-5-yl)-benzamide;
[4-Amino-*N*-methyl-3-(1*H*-tetrazol-5-yl)-benzoylamino]-acetic acid;
3-[4-Amino-3-(1*H*-tetrazol-5-yl)-phenyl]-*N*-methyl-propionamide;
N-[4-Amino-3-(1*H*-tetrazol-5-yl)-phenyl]-benzamide.

Example 18

***N*-(3,5-Bis-trifluoromethyl-phenyl)-*N*′-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4′-carboxylic acid dimethylamide] urea**

2′-Amino-3′-(1*H*-tetrazol-5-yl)-biphenyl-4-carboxylic acid dimethylamide (1 g, 3.2 mmol) in toluene (25 ml) was added 3,5-bis-(trifluoromethyl)-phenyl isocyanate (0.88 g, 3.3 mmol, app 1 eq.) and triethylamine (0.36 g, 3.6 mmol, 1.2 eq.), the reaction mixture was stirred overnight, an oil in the bottom of the flask was isolated. The oil was dissolved in 2-propanol (20 ml), the solution was added hydrochloric acid (1M) until pH = 2-3, the title compound precipitated. Yield 0.86 g. M.p. 222-224°C.

The following compounds were made analogously:
N-(3-Chloro-4-fluoro-phenyl)-*N*′-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4′-sulfonic acid-dimethylamide] urea; Mp. 240-243°C;
N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N*′-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4′-sulfonic acid-dimethylamide] urea; Mp. 254-258°C;
N-(3-Fluoro-5-trifluoromethyl-phenyl)-*N*′-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4′-sulfonic acid-dimethylamide] urea; M.p. 255-256°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*′-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4′-sulfonic acid-dimethylamide] urea; M.p.203-205°C;
N-(3,5-Difluoro-phenyl)-*N*′-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4′-sulfonic acid-dimethylamide] urea; M.p. 254-255°C;
N-(3,5-Dichloro-phenyl)-*N*′-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4′-carboxylic acid dimethylamide] urea; M.p. 201-204°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*′-[2-bromo-4-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 229-233°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*′-[2,6-dibromo-3-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 220-222°C;
4-Chloro-2-(3-cyclohexyl-ureido)-benzoic acid; M.p.
N-Cyclohexyl-*N*′-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;

[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-pyrroline-2-carboxylic acid;
1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrroline-2-carboxylic acid;
N-Cyclohexyl-*N'*-(2,3-difluoro-phenyl) urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[2-bromo-5-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(Cyclohexyl)-*N'*-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid;
2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid;
[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(5-trifluoromethyl-phenyl)-acetic acid;
5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3-bromo-phenyl)-ureido]-benzoic acid;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
[3-(4-Chloro-3-fluoro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
N-(3-Bromo-phenyl)-*N'*-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N'*-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3-Chloro-phenyl)-*N'*-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
[3-(3,5-Dichloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-(phenyl-2-boronic acid) urea;
N-(4-Chloro-3-fluoro-phenyl)-*N'*-(phenyl-2-boronic acid) urea;
N-(3,5-Dichloro-phenyl)-*N'*-(phenyl-2-boronic acid) urea;
N-Cyclohexyl-*N'*-(phenyl-2-boronic acid) urea;
N-(2,6-Dichlooro-pyridin-4-yl)-*N'*-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 201-203°C;
N-Cyclohexyl-*N'*-[4'-(*N''*,*N''*-dimethyl-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea; M.p. 156-158°C;
N-(2,6-Dichloro-pyridin-4-yl)-*N'*-[4'-(*N''*,*N''*-dimethyl-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea; M.p. 163.8-164.5°C;
N-Cyclohexyl-*N'*-[4-bromo-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 233-239°C;
N-(2,6-Dichloro-pyridin-4-yl)-*N'*-[4-bromo-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 231-233°C;
5-Chloro-2-[3-(pyridin-3-yl)-ureido]-benzoic acid; M.p. > 240°C;
5-Bromo-2-[3-(pyridin-3-yl)-ureido]-benzoic acid; M.p. > 240°C;
3,5-Dichloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid; M.p. 259-261°C;
3,5-Dichloro-2-[3-(3-chloro-4-fluoro-phenyl)-ureido]-benzoic acid; M.p.174.5-175.9°C;
3,5-Dichloro-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid; M.p.199-200°C;

3,5-Dichloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid; M.p.190.3-191.1°C;
3,5-Dichloro-2-[3-(4-fluoro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid; M.p. 180-181°C;
3,5-Dichloro-2-[3-(3-fluoro-5-trifluoromethyl-phenyl)-ureido]-benzoic acid; M.p. 168-169°C;
3,5-Dichloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid; M.p. 245-249°C;
N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[2,4-dibromo-6-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 195-196°C;
N-(3,4-Dichloro-phenyl)-*N'*-[2,4-dibromo-6-(1*H*-tetrazol-5-yl)-phenyl] urea; 201-203°C;
2-[3-(Thiophen-2-yl)-ureido]-benzoic acid;
2-[3-(Pyridin-4-yl)-ureido]-benzoic acid; M.p.> 230°C;
4-Chloro-2-[3-(pyridin-4-yl)-ureido]-benzoic acid; M.p. > 270°C;
5-Bromo-2-[3-(pyridin-4-yl)-ureido]-benzoic acid;
2-[3-(Pyridin-3-yl)-ureido]-nicotinic acid; M.p. > 220°C;
1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 159-161°C;
1-(3-Chloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 157-158°C;
1-(3-Bromo-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 176-177°C;
1-(3,5-Dichloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 180-181°C;
1-(Cyclohexyl-carbamoyl)-pyrrolidine-2-carboxylic acid; M.p 172-174°C;
1-(2,6-Dichloro-pyridin-4-ylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 177-178°C;
2-[(3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 194-195°C;
2-[(3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p 199-200°C;
2-[3-(3,5-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 141-142°C;
2-(3-Cyclohexyl-ureido)-cyclohexanecarboxylic acid; M.p. 190-191°C;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexane carboxylic acid; M.p. 199-200°C;
4-Chloro-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid; M.p. 200-201°C;
5-Bromo-2-[3-(3-chloro-phenyl)-ureido]-benzoic acid; M.p. 194-195°C;
2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
N-(2,3-Difluoro-4-trifluoromethyl-phenyl)-*N'*-(pyridin-3-yl) urea; M.p. 232-235°C;
N-[5-Chloro-2-(1*H*-tetrazol-5-yl)-phenyl]-*N'*-(pyridin-3-yl) urea; M.p. 214-220°C;
N-(Pyridin-3-yl)-*N'*-(2,3-difluoro-phenyl) urea; M.p. 211-215°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-(2,3-difluoro-4-trifluoromethyl-phenyl) urea; M.p. 194-195°C;
N-(2,6-Dichloro-pyridin-4-yl)-*N'*-(2,3-difluoro-4-trifluoromethyl-phenyl) urea; M.p. 210-211°C;
N-[4-Bromo-2-(1*H*-tetrazol-5-yl)-phenyl]-*N'*-(pyridin-3-yl) urea; M.p. 193-194°C;
2-[3-(Pyridin-3-yl)-ureido]-phenyl-boronic acid; M.p. 220-227°C;

5-Bromo-2-(3-cyclohexyl-ureido)-benzoic acid; M.p. 178-179°C;
[3-(3-Chloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid; M.p. 153-187°C;
N-(2,3-Difluoro-4-trifluoromehyl-phenyl)-*N'*-(pyridin-4-yl) urea; M.p. 205-206°C;
N-(2,3-Difluoro-phenyl)-*N'*-(pyridin-4-yl) urea; M.p. 201-215°C;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl-boronic acid; M.p. 232-233°C;
2-[3-(3-Bromo-phenyl)-ureido]-phenyl-dihydroxy-borane; M.p. 226-227°C;
2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 213-214°C;
2-[3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 173-178°C;
2-[3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 175-223°C;
2-[3-(2,6-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid; M.p. 182-241°C;
1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid; M.p. 67-80°C;
1-(3-Chloro-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid; M.p. 156-157°C;
1-(3-Bromo-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
1-(Pyridin-3-ylcarbamoyl)-pyrrolidine-2-carboxylic acid; M.p. 185-186°C;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexanecarboxylic acid; M.p. 168-197°C;
4-Chloro-2-[3-(thiazol-2-yl)-ureido]-benzoic acid methyl ester;
5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid methyl ester;
4-Chloro-2-[3-(5-chloro-pyridin-2-yl)-ureido]benzoic acid;
5-Bromo-2-(3-thiazol-2-yl-ureido)-benzoic acid methyl ester;
2-[3-(5-Bromo-pyridin-3-yl)-ureido]-4-chloro-benzoic acid; M.p. >220°C;
5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid;
{2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
N-(3-Methoxy-phenyl)-*N'*-[4'-(*N''*,*N''*-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2-Methoxy-phenyl)-*N'*-[4'-(*N''*,*N''*-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Methoxy-phenyl)-*N'*-[4'-(*N''*,*N''*-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(Naphthalen-1-yl)-*N'*-[4'-(*N''*,*N''*-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2-Trifluoromethyl-phenyl)-*N'*-[4'-(*N''*,*N''*-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4'-(*N''*,*N''*-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;

N-[2,4-Dibromo-6-(1*H*-tetrazol-5-yl)-phenyl]-*N'*-(2,6-dichloro-pyridin-4-yl) urea; M.p. 202-203°C;

N-(3,5-Dichloro-phenyl)-*N'*-[2,4-dibromo-6-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 221-223°C;

3-Bromo-2-[3-(2*H*-1λ^4-thiazol-2-yl)-ureido]-benzoic acid; M.p. >250°C;

{2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. 90-197°C;

{2-[3-(3-Chloro-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester; M.p. oil;

{2-[3-(3-Bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. oil;

{2-[3-(3,5-Dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. 156-158°C;

{5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. 152-158°C;

{5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. oil;

{5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. 160-207°C;

{5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p.145-250°C;

{5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester; M.p. 139-144°C;

{5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid diethyl ester;

2-{[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 205-206°C;

2-{[3-(3,5-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 195-196°C;

2-[(3-Phenyl-ureido)-benzyl]-phosphonic acid dimethyl ester;

2-[3-(4-Chloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 200-202°C;

2-{[3-(3,4-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 197-198°C;

{5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 210-211°C;

{5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 201-205°C;

[5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid dimethyl ester; M.p. 193-197°C;

{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;

{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester; M.p. 208-212°C;

2,5-Dichloro-3-[3-(3-bromo-phenyl)-ureido]-benzoic acid; M.p. 254-255°C;
2,5-Dichloro-3-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid; M.p. 256-257°C;
{2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid diethyl ester; M.p. 166-167°C;
{2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester; M.p. oil;
5-Chloro-2-[3-(1*H*-indol-2-yl)-ureido]-benzoic acid; M.p. > 200°C;
5-Bromo-2-[3-(1*H*-indol-2-yl)-ureido]-benzoic acid; M.p > 230°C;
3-[3-(3-Bromo-phenyl)-ureido]-5-trifluoro-benzoic acid; M.p. 230-231°C;
3-[3-(3,5-Dichloro-phenyl)-ureido]-5-trifluoro-benzoic acid; M.p. 218-233°C;
3-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide; M.p. 210-211°C;
3-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
3-[3-(2,3-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
3-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
4-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Difluoro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(2-Chloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4'-(piperidine-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Dichloro-phenyl)-*N'*-[4'-(piperidine-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4'-(piperidine-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Difluoro-phenyl)-*N'*-[4'-(piperidine-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2-Chloro-phenyl)-*N'*-[4'-(piperidine-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
4-Chloro-2-[3-(5-phenyl-2*H*-pyrazol-3-yl)-ureido]-benzoic acid; M.p > 270°C;
2-[3-(2-chloro-pyridin-3-yl)-ureido]-nicotinic acid; M.p. > 260°C;
4-Chloro-2-[3-(2-chloro-pyridin-3-yl)-ureido]-benzoic acid; M.p. > 215°C;
2-[3-(4-Chloro-phenyl)-ureido]-5-iodo-benzoic acid; M.p. > 200 °C;
5-Chloro-2-[3-(5-oxo-1-phenyl-pyrrolidin-3-yl)-ureido]-benzoic acid; M.p. > 240°C;
5-Bromo-2-(3-phenyl-ureido)-benzoic acid; M.p. > 200°C;
5-Bromo-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid; M.p. > 200°C;
5-Bromo-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid; M.p. > 220°C;
5-Bromo-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid; M.p. > 210°C;
5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid; M.p. 214-215°C;
5-Bromo-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid; M.p. 194-195°C;

N-(3,5-Dichloro-phenyl)-*N'*-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 205-207°C;
N-(3,5-Difluoro-phenyl)-*N'*-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 212-214°C;
5-Bromo-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid; M.p. > 225°C;
5-Bromo-2-[3-(2-bromo-phenyl)-ureido]-benzoic acid; M.p. > 225°C;
5-Bromo-2-[3-(4-chloro-3-nitro-phenyl)-ureido]-benzoic acid; M.p. > 230°C;
5-Bromo-2-[3-(4-butoxy-phenyl)-ureido]-benzoic acid; M.p. > 195°C;
5-Chloro-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid; M.p. > 210°C;
5-Chloro-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid; M.p. > 200°C;
2-[3-(4-Biphenyl)-ureido]-5-bromo-benzoic acid; M.p. > 200°C;
5-Chloro-2-[3-(3-iodo-phenyl)-ureido]- -benzoic acid; M.p. > 210°C;
5-Chloro-2-(3-phenyl-ureido)-benzoic acid; M.p. > 195°C;
5-Chloro-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid; M.p. > 195°C;
N-(3,5-Bis-trifluoromethyl)-*N'*-[2,4-dichloro-5-(1*H*-tetrazol-5yl)-phenyl] urea; M.p. > 200-203°C;
5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-nicotinic acid; M.p. > 300°C;
N-(3,5-Dichloro-phenyl)-*N'*-[4-(*N''*-methyl-carboxamide)- 2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 276-277°C;
N-(3,5-Difluoro-phenyl)-*N'*-[4-(*N''*-methyl-carboxamide)- 2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 277-278°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4-(carbonyl-amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 187-191°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4-(acrylic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 244-248°C;
N-(3,5-Dichloro-phenyl)-*N'*-[4-(acrylic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 237-245°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4-(acrylic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N'*-[4-(acrylic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 257-258°C;
N-(2-Chloro-phenyl)-*N'*-[4-(acrylic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 184-185°C;
N-(4-Chloro-3-trifluoro-phenyl)-*N'*-[4-(propionic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 168-169°C;
N-(3,5-Dichloro-phenyl)-*N'*-[4-(propionic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 169-177°C;

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4-(propionic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 194-195°C;
N-(3,5-Difluoro-phenyl)-*N'*-[4-(propionic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 173-177°C;
N-(2-Chloro-phenyl)-*N'*-[4-(propionic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 228-229°C;
5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid; M.p. > 300°C;
N-(3,5-Dichloro-phenyl)-*N'*-[4-(*N''*-malonamic acid)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 223-225°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4-(*N''*-malonamic acid)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 172-175°C;
N-(3,5-Difluoro-phenyl)-*N'*-[4-(*N''*-malonamic acid)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 170-173°C;
N-(2-Chloro-phenyl)-*N'*-[4-(*N''*-malonamic acid)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 158-160°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-{4-[(*N''*,*N''*-dimethyl)-acrylamide]-2-(1*H*-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Difluoro-phenyl)-*N'*-{4-[(*N''*,*N''*-dimethyl)-acrylamide]-2-(1*H*-tetrazol-5-yl)-phenyl} urea;
N-(2-Chloro-phenyl)-*N'*-{4-[(*N''*,*N''*-dimethyl)-acrylamide]-2-(1*H*-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Dichloro-phenyl)-*N'*-{4-[(*N''*-methyl)-acrylamide]-2-(1*H*-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Difluoro-phenyl)-*N'*-{4-[(*N''*-methyl)-acrylamide]-2-(1*H*-tetrazol-5-yl)-phenyl} urea;
N-(2-Chloro-phenyl)-*N'*-[4-(piperidine-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N'*-[4-(*N''*,*N''*-diethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4-(*N''*,*N''*-diethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N'*-[4-(*N''*,*N''*-diethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-*N'*-[4-(*N''*,*N''*-diethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 174-177°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4-(piperidine-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 210-212°C;
N-(3,5-dichloro-phenyl)-*N'*-[4-(piperidine-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 192-196°C;

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4-(piperidine-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 189-190°C;
N-(3,5-Difluoro-phenyl)-*N'*-[4-(piperidine-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 183-185°C;
N-(3,5-Dichloro-phenyl)-*N'*-[4'-(carbonyl-(*N''*-methyl)amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea; M.p. 286-287°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4'-carboxamide-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea; M.p. 245-247°C;
N-(3,5-Dichloro-phenyl)-*N'*-[4'-carboxamide-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4'-carboxamide-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea; M.p. 190-244°C;
N-(3,5-Difluoro-phenyl)-*N'*-[4'-carboxamide-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Dichloro-phenyl)-*N'*-[4-(*N''*,*N''*-dimethyl-caboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 184-244°C;
N-(3,5-Difluoro-phenyl)-*N'*-[4-(*N''*,*N''*-dimethyl-caboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 183-198°C;
N-(4-Chloro-3-trifluoromethyl)-*N'*-[4-(*N''*,*N''*-diethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p.191-240°C;
N-(3,5-Dichloro-phenyl)-*N'*-[4'-(carbonyl-amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea; M.p. 265-266°C;
N-(3,5-Difluoro-phenyl)-*N'*-[4'-(carbonyl-amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea; M.p. 235-242°C;
N-(2-Chloro-phenyl)-*N'*-[4'-(carbonyl-amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea; M.p. 253-254°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-{4'-[carbonyl-(*N''*-methyl)-amino-acetic acid]-2-(1*H*-tetrazol-5-yl)-4-biphenyl} urea; M.p. 249-250°C;
N-(3,5-Dichloro-phenyl)-*N'*-{4'-[carbonyl-(*N''*-methyl)-amino-acetic acid]-2-(1*H*-tetrazol-5-yl)-4-biphenyl} urea; M.p. 251-286°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-{4'-[carbonyl-(*N''*-methyl)-amino-acetic acid]-2-(1*H*-tetrazol-5-yl)-4-biphenyl} urea; M.p. 190-191°C;
N-(3,5-Difluoro-phenyl)-*N'*-[4'-(carbonyl-amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea; M.p. decomp.;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4-(*N''*-methyl-propylamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N'*-[4-(*N''*-methyl-propyamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluromethyl-phenyl)-*N'*-[4-(*N''*-methyl-propylamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Difluoro-phenyl)-*N'*-[4-(*N''*-methyl-propylamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-chloro-phenyl)-*N'*-[4-(*N''*-methyl-propylamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
5-Chloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[(3,4-dichloro-phenyl)-ureido]-benzoic acid;
2-[3-(4-Butoxy-phenyl)-ureido]-5-chloro- benzoic acid;
5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-nicotinic acid; M.p > 300°C;
5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-nicotinic acid; M.p > 300°C;
N-(2,6-Dichloro-phenyl)-*N'*-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 214-215°C;
N-(2,4,6-trichloro-phenyl)-*N'*-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 207-209°C;
5-Bromo-2-[3-(2,4,6-trichloro-phenyl)-ureido]-nicotinic acid; M.p. > 300°C;
N-(3,5-Dichloro-phenyl)-*N'*-[4-benzamide-2-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 238-239°C;
N-(3,5-Difluoro-phenyl)-*N'*-[4-benzamide-2-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 254-256°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4-benzamide-2-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 250-253°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)- *N'*-[4-benzamide-2-(1*H*-tetrazol-5-yl)-phenyl) urea; M.p. 248-250°C;
5-Chloro-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid. M.p. > 300°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4'-(*N''*-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea; M.p. 244-245°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)- *N'*-[4-(*N'',N''*-dimethyl acryl-amide)-2-(1-*H*-tetrazol-5-yl)-phenyl] urea; M.p. 169-171°C;
N-(3,5-dichloro-phenyl)-*N'*-[4-(*N'',N''*-dimethyl acryl-amide)-2-(1-*H*-tetrazol-5-yl)phenyl] urea; M.p. 190-193°C;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4'-(*N''*-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea; M.p. 275-296°C;

Example 19

3,5-Bis-[3-(3-bromo-phenyl)-ureido]-benzoic acid

3,5-Diaminobenzoic acid (152 mg, 1 mmol) in anhydrous acetonitrile (5 ml) under an argon atmosphere was added 3-bromophenyl isocyanate (396 mg, 2 mmol, 2 eq.). The reaction mixture was stirred at 60 °C for 16 hours. The title compound precipitated out of solution and was isolated by filtration. Yield 377 mg. M.p. > 300°C.

The following compounds were made analogously:

3,5-Bis-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid; M.p. > 300°C;
3,5-Bis-[3-(3,5-difluro-phenyl)-ureido]-benzoic acid; M.p. > 300°C;
3,5-Bis-[3-(3,5-bis-trifluoromethylphenyl)-ureido]-benzoic acid; M.p. > 300°C.

Example 20

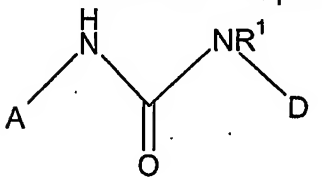
{2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid

{2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester (400 mg, 0.8 mmol) was dissolved in anhydrous dichloromethane (3 ml). Under a argon atmosphere was added trimethylsilyl bromide (2 ml, 15 mmol, 19 eq.), the reaction mixture was heated at reflux overnight then evaporated to dryness, to the residue was added water (10 ml) and ethyl acetate (10 ml), the organic layer was separated, dried and evaporated. The title compound was crystallized from dichloromethane. Yield 340 mg, M.p. 153-157°C.

The following compounds were made analogously:
{2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 147-149°C;
{2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 145-151°C;
{2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 167-170°C;
{5-Bromo-2-[3-(3,5 bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 150-153°C;
{5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 267-273°C;
{5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 160-207°C;
{5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 204-210°C;
{5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid; M.p. 212-288°C;
{5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid;
2-{[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 185-197°C;
2-{[3-(3,5-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 192-193°C;
2-[(3-Phenyl-ureido)-benzyl]-phosphonic acid; M.p. 166-168°C;
2-[3-(4-Chloro-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 184-191°C;
2-{[3-(3,4-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 177-178°C;
{5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 177-180°C;
{5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid; Mp. 181-182°C;
[5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid; M.p. 174-182°C;
{5-Chloro-2-[3-(4-chloro-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 189-190°C;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid; M.p. 191-192°C;
{2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid; M.p. 185-189°C;
{2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid; M.p. 155-162°C.

CLAIMS:

1. A chemical compound represented by general formula (I)

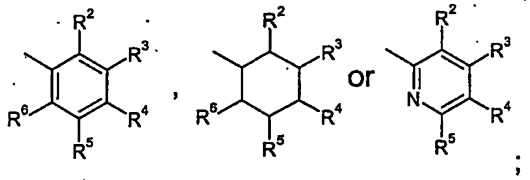


(I)

or a pharmaceutically acceptable salt thereof, wherein

A represents a ring system selected from the group consisting of:
cyclohexanyl, phenyl, pyridyl, thienyl, thiazolyl, naphthyl, indolyl, pyrazolyl and oxo-pyrrolidinyl;
which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:
halo, trifluoromethyl, nitro, alkyl, alkoxy, and phenyl; and

R^1 represents -H; and
D represents



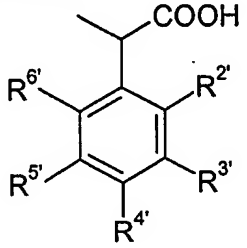
;

wherein
one of R^2, R^3, and R^4 is selected from the group consisting of:
tetrazolyl, $-COOR^a$, $-B(OH)_2$, $-PO(OR^a)_2$, $-CH_2-PO(OR^a)_2$, and -CONH;
wherein R^a is hydrogen or alkyl;
or R^2 and R^3 or R^3 and R^4 both represent fluoro; and
R^5, R^6 and the remaining one or two of R^2, R^3 and R^4 independently of each other represent:

- hydrogen, halo, trifluoromethyl,
- $-CH=CH-COOR^b$, $-CH_2-CH_2-COOR^b$,
- $-CO-NR^b-CH_2-COOR^c$; $-CO-NR^bR^c$,
- $-CH=CH-CO-NR^bR^c$; $-CH_2-CH_2-CO-NR^bR^c$,
- piperidylcarbonyl,
- $-NH-CO-R^d$ or $-NH-CO-NH-R^d$;
  wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halo or trifluoromethyl; or
- phenyl optionally substituted with

$-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;
wherein R^b and R^c independently are hydrogen or alkyl;

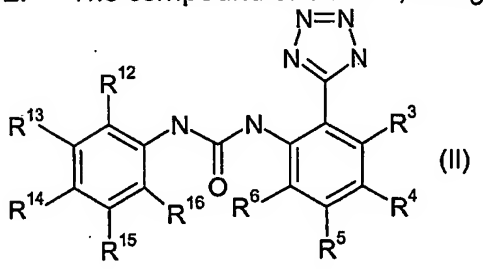
or R^1 represents -H; and
D represents



wherein $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, $R^{6'}$ independently of each other represent hydrogen, halo, or trifluoromethyl:

or R^1 together with D forms $-CHR^e-CH_2-CHR^f-CH_2-$;
wherein R^e represents -COOH;
R^f represents hydrogen or hydroxy.

2. The compound of claim 1, being a compound of general formula (II)



(II)

or a pharmaceutically acceptable salt thereof, wherein

R^3, R^4, R^5 and R^6 independently of each other represent:

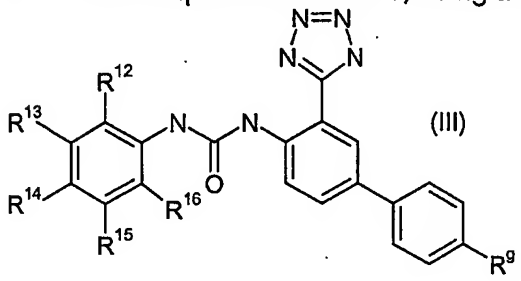
- hydrogen, halo, trifluoromethyl,
- $-CH=CH-COOR^b$, $-CH_2-CH_2-COOR^b$,
- $-CO-NR^b-CH_2-COOR^c$; $-CO-NR^bR^c$,
- $-CH=CH-CO-NR^bR^c$; $-CH_2-CH_2-CO-NR^bR^c$,
- piperidylcarbonyl,
- $-NH-CO-R^d$ or $-NH-CO-NH-R^d$;
  wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halo or trifluoromethyl (bromo, dichloro); or
- phenyl optionally substituted with
  $-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl;

R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} independently of each other represent hydrogen, halo, trifluoromethyl, nitro, alkyl, or alkoxy.

3. The compound of claim 2, wherein
R^4 and R^6 each represent halo;
R^2, R^3, and R^5 each represent hydrogen;
two or three of R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} independently of each other represent halo; and
the remaining three or two of R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} represent hydrogen.

4. The compound of claim 1, being a compound of general formula (III)



or a pharmaceutically acceptable salt thereof, wherein

R^9 represents -CO-NR^bR^c, -CO-NR^b-CH_2-$COOR^c$, or piperidylcarbonyl;
wherein R^b and R^c independently are hydrogen or alkyl;

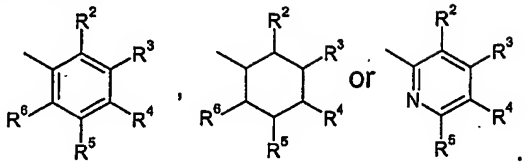
two of R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} independently of each other represent halo, trifluoromethyl, nitro, alkyl, or alkoxy;
and the remaining three of R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} represent hydrogen.

5. The compound of claim 4, wherein
R^9 represents -CO-NR^bR^c;
wherein R^b and R^c independently are hydrogen or alkyl;
R^{13} and R^{15} represent halo; and
R^{12}, R^{14} and R^{16} each represent hydrogen.

6. The formula of claim 1, wherein
A represents a ring system selected from the group consisting of:
cyclohexanyl, phenyl, pyridyl, thienyl, thiazolyl, and pyrazolyl;
which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:
halo, trifluoromethyl, nitro, alkyl, alkoxy, and phenyl; and

R^1 represents -H; and

D represents



;

wherein

R^2 represents $-COOR^a$;

wherein R^a is hydrogen or alkyl;

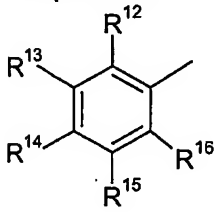
R^3, R^4, R^5, and R^6 independently of each other represent:

- hydrogen, halo, trifluoromethyl,
- $-NH-CO-R^d$ or $-NH-CO-NH-R^d$;
  wherein R^d is phenyl optionally substituted with one or more substituents independently selected from halo or trifluoromethyl; or
- phenyl optionally substituted with
  $-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$; or piperidylcarbonyl;

wherein R^b and R^c independently are hydrogen or alkyl.

7. The compound of claim 6, wherein

A represents



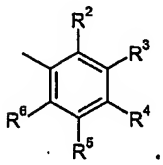
wherein R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} independently of each other represent:
halo, trifluoromethyl, nitro, alkyl, alkoxy, or phenyl.

8. The compound of claim 1, wherein

A represents a ring system selected from the group consisting of:
cyclohexanyl, phenyl, and pyridyl;
which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:
halo, trifluoromethyl, nitro, alkyl, and alkoxy; and

R^1 represents -H; and

D represents



;

wherein

R^2 represents $-B(OH)_2$, $-PO(OR^a)_2$, $-CH_2-PO(OR^a)_2$, or -CONH;

wherein R^a is hydrogen or alkyl (hydrogen, methyl, ethyl);

R^2, R^3, R^4, R^5, and R^6 independently of each other represent:

hydrogen, halo, trifluoromethyl, or phenyl.

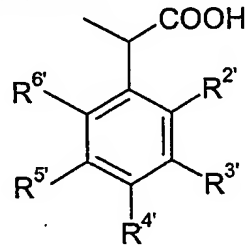
9. The compound of claim 1, wherein

A represents phenyl optionally substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, nitro, alkyl, and alkoxy; and

R^1 represents -H; and

D represents



wherein $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, $R^{6'}$ independently of each other represent hydrogen, halo, or trifluoromethyl.

10. The compound of claim 1, wherein

A represents a ring system selected from the group consisting of:

cyclohexanyl, phenyl, and pyridyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, nitro, alkyl, and alkoxy; and

R^1 together with D forms $-CHR^e-CH_2-CHR^f-CH_2-$;

wherein R^e represents -COOH;

R^f represents hydrogen or hydroxy.

11. The compound of claim 1, wherein

A represents a ring system selected from the group consisting of:

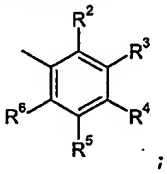
cyclohexanyl, phenyl, and pyridyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, nitro, alkyl, and alkoxy;

R^1 represents -H; and

D represents



;

wherein

R^2 and R^3 or R^3 and R^4 both represent fluoro; and

R^5, R^6 and the remaining one or two of R^2, R^3 and R^4 independently of each other represent hydrogen, halo, or trifluoromethyl.

12. The compound of claim 1, wherein

A represents a ring system selected from the group consisting of:

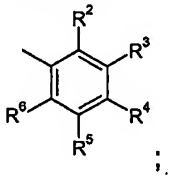
cyclohexanyl, pyridyl, and naphthyl;

which ring system is optionally substituted with one or more substituents independently selected from the group consisting of:

halo, trifluoromethyl, nitro, alkyl, and alkoxy; and

R^1 represents -H; and

D represents



;

wherein

R^2 represents tetrazolyl;

R^3, R^4, R^5, and R^6 independently of each other represent:

- hydrogen, halo, trifluoromethyl; or
- phenyl substituted with

  $-SO_2-NR^bR^c$, $-CO-NR^bR^c$, $-CO-NR^b-CH_2-COOR^c$, or piperidylcarbonyl;

  wherein R^b and R^c independently are hydrogen or alkyl (methyl).

13. The compound of claim 1, being

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[2-bromo-4-(1*H*-tetrazol-5-yl)-phenyl urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[2,6-dibromo-3-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[2-bromo-5-(1*H*-tetrazol-5-yl)-phenyl] urea;
5-Chloro-2-[3-(1*H*-indol-2-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(1*H*-indol-2-yl)-ureido]-benzoic acid;
N-(3-Fluoro-5-trifluoromethyl-phenyl)-*N*´-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4´-sulfonic acid-dimethylamide] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4´-sulfonic acid-dimethylamide] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4´-sulfonic acid-dimethylamide] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3-Bromo-phenyl)-*N*´-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3-Chloro-phenyl)-*N*´-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N*´-[2,4-dibromo-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,4-Dichloro-phenyl)-*N*´-[2,4-dibromo-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3-Methoxy-phenyl)-*N*´-[4´-(*N*´´,*N*´´-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2-Methoxy-phenyl)-*N*´-[4´-(*N*´´,*N*´´-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Methoxy-phenyl)-*N*´-[4´-(*N*´´,*N*´´-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2-Trifluoromethyl-phenyl)-*N*´-[4´-(*N*´´,*N*´´-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-[4´-(*N*´´,*N*´´-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[2,4-dibromo-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-*N*´-[4´-(piperidine-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl)-*N*´-[2,4-dichloro-5-(1*H*-tetrazol-5yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[4-(*N*´´-methyl-carboxamide)- 2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4-(*N*´´-methyl-carboxamide)- 2-(1*H*-tetrazol-5-yl)-phenyl] urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-[4-(carbonyl-amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-[4-(acrylic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[4-(acrylic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[4-(acrylic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4-(acrylic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-*N*´-[4-(acrylic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoro-phenyl)-*N*´-[4-(propionic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[4-(propionic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[4-(propionic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4-(propionic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-*N*´-[4-(propionic acid methyl ester)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N*´-[4-(*N*´´-malonamic acid)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-[4-(*N*-malonamic acid)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N*´-[4-(*N*´´-malonamic acid)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-*N*´-[4-(*N*´´-malonamic acid)-2-(1*H*-tetrazol-5-yl)-phenyl] urea; M.p. 158-160°C;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N*´-{4-[(*N*´´,*N*´´-dimethyl)-acrylamide]-2-(1*H*-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Difluoro-phenyl)-*N*´-{4-[(*N*´´,*N*´´-dimethyl)-acrylamide]-2-(1*H*-tetrazol-5-yl)-phenyl} urea;
N-(2-Chloro-phenyl)-*N*´-{4-[(*N*´´,*N*´´-dimethyl)-acrylamide]-2-(1*H*-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Dichloro-phenyl)-*N*´-{4-[(*N*´´-methyl)-acrylamide]-2-(1*H*-tetrazol-5-yl)-phenyl} urea;
N-(3,5-Difluoro-phenyl)-*N*´-{4-[(*N*´´-methyl)-acrylamide]-2-(1*H*-tetrazol-5-yl)-phenyl} urea;
N-(2-Chloro-phenyl)-*N*´-[4-(piperidine-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;

N-(3,5-Dichloro-phenyl)-*N'*-[4-(*N''*,*N''*-diethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4-(*N''*,*N''*-diethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N'*-[4-(*N''*,*N''*-diethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-*N'*-[4-(*N''*,*N''*-diethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4-(piperidine-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-dichloro-phenyl)-*N'*-[4-(piperidine-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4-(piperidine-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N'*-[4-(piperidine-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N'*-[4'-(carbonyl-(*N''*-methyl)amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Dichloro-phenyl)-*N'*-[4-(*N''*,*N''*-dimethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N'*-[4-(*N''*,*N''*-dimethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(4-Chloro-3-trifluoromethyl)-*N'*-[4-(*N''*,*N''*-diethyl-carboxamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-Chloro-phenyl)-*N'*-[4'-(carbonyl-amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4-(*N''*-methyl-propylamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N'*-[4-(*N''*-methyl-propyamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluromethyl-phenyl)-*N'*-[4-(*N''*-methyl-propylamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N'*-[4-(*N''*-methyl-propylamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2-chloro-phenyl)-*N'*-[4-(*N''*-methyl-propylamide)-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2,6-Dichloro-phenyl)-*N'*-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2,4,6-trichloro-phenyl)-*N'*-[2,4-dichloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Dichloro-phenyl)-*N'*-[4-benzamide-2-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Difluoro-phenyl)-*N'*-[4-benzamide-2-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4-benzamide-2-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;

N-(4-Chloro-3-trifluoromethyl-phenyl)- *N'*-[4-benzamide-2-(1*H*-tetrazol-5-yl)-phenyl) urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)- *N'*-[4-(*N''*,*N''*-dimethyl acryl-amide)-2-(1-*H*-tetrazol-5-yl)-phenyl] urea;
N-(3,5-dichloro-phenyl)-*N'*-[4-(*N''*,*N''*-dimethyl acryl-amide)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-(3-Chloro-4-fluoro-phenyl)-*N'*-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea;
N-(4-Fluoro-3-trifluoromethyl-phenyl)-*N'*-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4'-sulfonic acid-dimethylamide] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4'-carboxylic acid dimethylamide] urea
N-(3,5-Dichloro-phenyl)-*N'*-[2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl-4'-carboxylic acid dimethylamide] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4'-(piperidine-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Dichloro-phenyl)-*N'*-[4'-(piperidine-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4'-(piperidine-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(3,5-Difluoro-phenyl)-*N'*-[4'-(piperidine-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4'-carboxamide-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Dichloro-phenyl)-*N'*-[4'-carboxamide-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4'-carboxamide-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Difluoro-phenyl)-*N'*-[4'-carboxamide-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Dichloro-phenyl)-*N'*-[4'-(carbonyl-amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Difluoro-phenyl)-*N'*-[4'-(carbonyl-amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-{4'-[carbonyl-(*N''*-methyl)-amino-acetic acid]-2-(1*H*-tetrazol-5-yl)-4-biphenyl} urea;
N-(3,5-Dichloro-phenyl)-*N'*-{4'-[carbonyl-(*N''*-methyl)-amino-acetic acid]-2-(1*H*-tetrazol-5-yl)-4-biphenyl} urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-{4'-[carbonyl-(*N''*-methyl)-amino-acetic acid]-2-(1*H*-tetrazol-5-yl)-4-biphenyl} urea;

N-(3,5-Difluoro-phenyl)-*N'*-[4'-(carbonyl-amino-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[4'-(*N''*-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N'*-[4'-(*N''*-acetic acid)-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea;
4-Chloro-2-(3-cyclohexyl-ureido)-benzoic acid;
5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid;
2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid;
5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3-bromo-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid;
N-(3,5-Bis-trifluormethyl-phenyl)-*N'*-(phenyl-2-boronic acid) urea;
N-(4-Chloro-3-fluoro-phenyl)-*N'*-(phenyl-2-boronic acid) urea;
N-(3,5-Dichloro-phenyl)-*N'*-(phenyl-2-boronic acid) urea;
N-Cyclohexyl-*N'*-(phenyl-2-boronic acid) urea;
5-Chloro-2-[3-(pyridin-3-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(pyridin-3-yl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3-chloro-4-fluoro-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(4-fluoro-3-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3-fluoro-5-trifluoromethyl-phenyl)-ureido]-benzoic acid;
3,5-Dichloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
2-[3-(Thiophen-2-yl)-ureido]-benzoic acid;
2-[3-(Pyridin-4-yl)-ureido]-benzoic acid;
4-Chloro-2-[3-(pyridin-4-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(pyridin-4-yl)-ureido]-benzoic acid;
2-[3-(Pyridin-3-yl)-ureido]-nicotinic acid;
2-[(3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[(3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(3,5-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-(3-Cyclohexyl-ureido)-cyclohexanecarboxylic acid;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexane carboxylic acid;
4-Chloro-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3-chloro-phenyl)-ureido]-benzoic acid;
2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid;

5-Bromo-2-(3-cyclohexyl-ureido)-benzoic acid;
2-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(3-Chloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(3-Bromo-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(2,6-Dichloro-phenyl)-ureido]-cyclohexanecarboxylic acid;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-cyclohexanecarboxylic acid;
4-Chloro-2-[3-(thiazol-2-yl)-ureido]-benzoic acid methyl ester;
5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid methyl ester;
4-Chloro-2-[3-(5-chloro-pyridin-2-yl)-ureido]benzoic acid;
5-Bromo-2-(3-thiazol-2-yl-ureido)-benzoic acid methyl ester;
2-[3-(5-Bromo-pyridin-3-yl)-ureido]-4-chloro-benzoic acid;
5-Bromo-2-[3-(pyridin-2-yl)-ureido]-benzoic acid;
3-Bromo-2-[3-(2*H*-1λ^4-thiazol-2-yl)-ureido]-benzoic acid;
3-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
4-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(3,5-Difluoro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-[3-(2-Chloro-phenyl)-ureido]-biphenyl-3-carboxylic acid;
4-Chloro-2-[3-(5-phenyl-2*H*-pyrazol-3-yl)-ureido]-benzoic acid;
2-[3-(2-chloro-pyridin-3-yl)-ureido]-nicotinic acid;
4-Chloro-2-[3-(2-chloro-pyridin-3-yl)-ureido]-benzoic acid;
2-[3-(4-Chloro-phenyl)-ureido]-5-iodo-benzoic acid;
5-Chloro-2-[3-(5-oxo-1-phenyl-pyrrolidin-3-yl)-ureido]-benzoic acid;
5-Bromo-2-(3-phenyl-ureido)-benzoic acid;
5-Bromo-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(2-bromo-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(4-chloro-3-nitro-phenyl)-ureido]-benzoic acid;
5-Bromo-2-[3-(4-butoxide-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(2-chloro-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(3,5-dimethyl-phenyl)-ureido]-benzoic acid;
2-[3-(4-Biphenyl)-ureido]-5-bromo-benzoic acid;
5-Chloro-2-[3-(3-iodo-phenyl)-ureido]- -benzoic acid;
5-Chloro-2-(3-phenyl-ureido)-benzoic acid;
5-Chloro-2-[3-(2-fluoro-phenyl)-ureido]-benzoic acid;

5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]-nicotinic acid;
5-Chloro-2-[3-(3,5-difluoro-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3-(3,5-dimethoxy-phenyl)-ureido]-benzoic acid;
5-Chloro-2-[3,4-dichloro-phenyl)-ureido]-benzoic acid;
2-[3-(4-Butoxy-phenyl)-ureido]-5-chloro- benzoic acid;
5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]-nicotinic acid;
3,5-Bis-[3-(3,5-difluro-phenyl)-ureido]- benzoic acid;
5-Bromo-2-[3-(3,5-difluoro-phenyl)-ureido]-nicotinic acid;
5-Bromo-2-[3-(2,4,6-trichloro-phenyl)-ureido]-nicotinic acid;
5-Chloro-2-[3-(2,6-dichloro-phenyl)-ureido]-benzoic acid;
3,5-Bis-[3-(3,5-bis-trifluoromethylphenyl)-ureido]- benzoic acid;
2,5-Dichloro-3-[3-(3-bromo-phenyl)-ureido]-benzoic acid;
2,5-Dichloro-3-[3-(3,5-dichloro-phenyl)-ureido]-benzoic acid;
3,5-Bis-[3-(3-bromo-phenyl)-ureido]- benzoic acid
3,5-Bis-[3-(3,5-dichloro-phenyl)-ureido]- benzoic acid;
3-[3-(3-Bromo-phenyl)-ureido]-5-trifluoro-benzoic acid;
3-[3-(3,5-Dichloro-phenyl)-ureido]-5-trifluoro-benzoic acid;
3,5-Bis-[3-(3,5-bis-trifluoromethylphenyl)-ureido]- benzoic acid;
2-[3-(Pyridin-3-yl)-ureido]-phenyl-boronic acid;
2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl-boronic acid;
2-[3-(3-Bromo-phenyl)-ureido]-phenyl-dihydroxy-borane;
{2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
{2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid
{2-[3-(3-chloro-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester;
{2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid;
{2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid;
{2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(3,5-bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(3,5 bis-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;

{5-Bromo-2-[3-(3-chloro-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(3-bromo-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(3,5-dichloro-phenyl)-ureido]phenyl}-phosphonic acid;
{5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid diethyl ester;
{5-Bromo-2-[3-(2,6-dichloro-pyridin-4-yl)-ureido]phenyl}-phosphonic acid;
2-{[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
2-{[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid;
2-{[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
2-{[3-(3,5-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
2-[(3-Phenyl-ureido)-benzyl]-phosphonic acid dimethyl ester;
2-[(3-Phenyl-ureido)-benzyl]-phosphonic acid;
2-[3-(4-Chloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
2-[3-(4-Chloro-phenyl)-ureido]-benzyl}-phosphonic acid;
2-{[3-(3,4-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
2-{[3-(3,4-Dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
{5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(4-chloro-3-trifluoromethyl-phenyl)-ureido]-benzyl}-phosphonic acid;
{5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(3,5-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
[5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid dimethyl ester;
[5-Chloro-2-(3-phenyl-ureido)-benzyl]-phosphonic acid;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(4-chloro-phenyl)-ureido]-benzyl}-phosphonic acid;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid dimethyl ester;
{5-Chloro-2-[3-(3,4-dichloro-phenyl)-ureido]-benzyl}-phosphonic acid;
{2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid diethyl ester;
{2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid diethyl ester;
{2-[3-(2-Trifluoromethyl-phenyl)-ureido]-phenyl}-phosphonic acid;
3-[3-(3,5-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
3-[3-(2,3-Dichloro-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
3-[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid amide;
{2-[3-(2,6-Dichloro-pyridin-4-yl)-ureido]-phenyl}-phosphonic acid;
[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
[3-(3,5-Bis-trifluoromethyl-phenyl)-ureido]-(5-trifluoromethyl-phenyl)-acetic acid;
[3-(4-Chloro-3-fluoro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;

[3-(3,5-Dichloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
[3-(3-Chloro-phenyl)-ureido]-(4-fluoro-phenyl)-acetic acid;
1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-pyrroline-2-carboxylic acid;
1-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrroline-2-carboxylic acid;
1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(3-Chloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(3-Bromo-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(3,5-Dichloro-phenylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(Cyclohexyl-carbamoyl)-pyrrolidine-2-carboxylic acid;
1-(2,6-Dichloro-pyridin-4-ylcarbamoyl)-pyrrolidine-2-carboxylic acid;
1-(4-Chloro-3-trifluoromethyl-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
1-(3-Chloro-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
1-(3-Bromo-phenylcarbamoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid;
1-(Pyridin-3-ylcarbamoyl)-pyrrolidine-2-carboxylic acid;
N-Cyclohexyl-*N*´-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
N-Cyclohexyl-*N*´-(2,3-difluoro-phenyl) urea;
N-(2,3-Difluoro-4-trifluoromethyl-phenyl)-*N*´-(pyridin-3-yl) urea;
N-(Pyridin-3-yl)-*N*´-(2,3-difluoro-phenyl) urea;
N-(4-Chloro-3-trifluoromethyl-phenyl)-*N*´-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
N-(2,6-Dichloro-pyridin-4-yl)-*N*´-(2,3-difluoro-4-trifluoromethyl-phenyl) urea;
N-(2,3-Difluoro-4-trifluoromehyl-phenyl)-*N*´-(pyridin-4-yl) urea;
N-(2,3-Difluoro-phenyl)-*N*´-(pyridin-4-yl) urea;
N-(Cyclohexyl)-*N*´-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2,6-Dichloro-pyridin-4-yl)-*N*´-[3-chloro-6-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-Cyclohexyl-*N*´-[4´-(*N*´´,*N*´´-dimethyl-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-(2,6-Dichloro-pyridin-4-yl)-*N*´-[4´-(*N*´´,*N*´´-dimethyl-1-carbonyl)-2-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-Cyclohexyl-*N*´-[4-bromo-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-(2,6-Dichloro-pyridin-4-yl)-*N*´-[4-bromo-2-(1*H*-tetrazol-5-yl)-phenyl] urea;
N-[5-Chloro-2-(1*H*-tetrazol-5-yl)-phenyl]-*N*´-(pyridin-3-yl) urea;
N-[4-Bromo-2-(1*H*-tetrazol-5-yl)-phenyl]-*N*´-(pyridin-3-yl) urea;
N-(Naphthalen-1-yl)-*N*´-[4´-(*N*´´,*N*´´-dimethyl-1-carbonyl)-3-(1*H*-tetrazol-5-yl)-biphenyl-4-yl] urea;
N-[2,4-Dibromo-6-(1*H*-tetrazol-5-yl)-phenyl]-*N*´-(2,6-dichloro-pyridin-4-yl) urea;
or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1-13, or a pharmaceutically acceptable salt

thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

15. The use of a compound according to any one of claims 1-13, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to the blockade of chloride channels.

16. The use according to claim 15, wherein the disease, disorder or condition responsive to the blockade of chloride channels is a bone metabolic disease or an osteoclast related bone disease.

17. The use according to claim 15, wherein the disease, disorder or condition responsive to the blockade of chloride channels is osteoporosis, postmenopausal osteoporosis, secondary osteoporosis, osteolytic breast cancer bone metastasis, osteolytic cancer invation, Paget's disease of bone.

18. The use according to claim 15, wherein the disease, disorder or condition responsive to the blockade of chloride channels is a disease, disorder or condition responsive to the mast cell or basophil activity, or to inhibition of angiogenesis.

19. The use according to claim 15, wherein the disease, disorder or condition responsive to the blockade of chloride channels is allergic bronchopulmonary aspergillosis (ABPA), allergic rhinitis, allergic skin disease, allergic skin reaction, drug induced allergic skin reaction, anaphylaxis, asthma, atherosclerosis, atopic dermatitis (AD), bronchial asthma, cancer, chronic obstructive pulmonary disease (COPD), Chrohn's disease, contact dermatitis, dilated cardiomyopathy, fatal asthma, graft rejection, hypersensitivity pneumonitis, ischemic hearth disease, pulmonary fibrosis, rheumatoid arthritis, systemic sclerosis, urticaria, uveoretinitis, cancer, metastatic cancer, prostate cancer, lung cancer, breast cancer, bladder cancer, renal cancer, colon cancer, gastric cancer, pancreatic cancer, ovarian cancer, melanoma, hepatoma, sarcoma, lymphoma, exudative macular degeneration, age-related mucular degeneration (AMD), retinopathy, diabetic retinopathy, proliferative diabetic retinopathy, ischemic retinopathy (e.g. retinal vain or artery occlusion), retinopathy of prematurity, neovascular glaucoma, corneal neovascularization, rheumatoid arthritis, psoriasis, sickle cell anaemia, brain oedema following ischaemia or tumors, diarrhea, hypertension, diuretic hypertension, glaucoma, or ulcers.

20. A method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to the blockade of chloride channels, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound according to any one of the claims 1-13, or any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof.

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(71) Applicant *(for all designated States except US)*: **NEUROSEARCH A/S** [DK/DK]; 93 Pederstrupvej, DK-2750 Ballerup (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DAHL, Bjarne, H.** [DK/DK]; Rådyrvænget 46, DK-3450 Allerød (DK). **CHRISTOPHERSEN, Palle** [DK/DK]; Axel Juels Allé 48, DK-2750 Ballerup (DK). **ENGSIG, Michael, Thyrring** [DK/DK]; Stengårds Allé 8, st., 0006, DK-2800 Kongens Lyngby (DK). **KARSDAL, Morten, Asser** [DK/DK]; Drejøgade 39, 4 tv, DK-2100 København Ø (DK). **FOGED, Niels, Tækker** [DK/DK]; Damvadvej 30, DK-3670 Veksø (DK). **JENSEN, Flemming, Reissig** [DK/DK]; Gustav Adolfs Gade 14, 4., DK-2100 København Ø (DK).

(74) Common Representative: **NEUROSEARCH A/S**; Patent Department, 93 Pederstrupvej, DK-2750 Ballerup (DK).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Declaration under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
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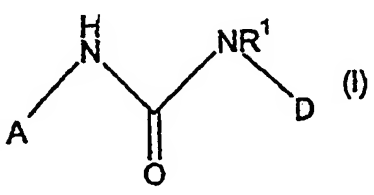
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DIARYLUREA DERIVATIVES AND THEIR USE AS CHLORIDE CHANNEL BLOCKERS



(I)

(57) Abstract: The present invention relates to novel diarylurea derivatives represented by general formula (I) useful as chloride channel blockers. In other aspects the invention relates to the use of these compounds in a method for therapy, such as for the treatment of bone metabolic diseases, diseases responsive to modulation of the mast cell or basophil activity, diseases responsive to inhibition of angiogenesis, or sickle cell anaemia, and to pharmaceutical compositions comprising the compounds of the invention.

WO 2004/022529 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00575

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C275/26 C07C275/28 C07D257/04 C07D207/00 A61K31/17
A61K31/41 A61P19/00 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03 000245 A (POSEIDON PHARMACEUTICALS AS ;DAHL BJARNE H (DK); MADSEN LARS SIIM) 3 January 2003 (2003-01-03) the whole document ---	1-20
X	WO 02 39987 A (DAHL BJARNE H ;NEUROSEARCH AS (DK); CHRISTOPHERSEN PALLE (DK)) 23 May 2002 (2002-05-23) the whole document ---	1-20
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	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 December 2003	26. 03. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	GERD STRANDELL /EÖ

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00575

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 24707 A (DAHL BJARNE H ;NEUROSEARCH AS (DK); CHRISTOPHERSEN PALLE (DK)) 4 May 2000 (2000-05-04) the whole document	1-20
X	WO 97 45400 A (NEUROSEARCH AS ;PEDERSEN OVE (DK); CHRISTOPHERSEN PALLE (DK)) 4 December 1997 (1997-12-04) the whole document	1-20
X	WO 02 064128 A (JAEAETTELAE MARJA ;LADEMANN ULRIK (DK); NEUROSEARCH AS (DK); PETER) 22 August 2002 (2002-08-22) claim 3	1-14
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INTERNATIONAL SEARCH REPORT

International application No:
PCT/DK 03/00575

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 20
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 20

Claim 20 relates to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practiesed on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds or compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/DK 03/00575

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